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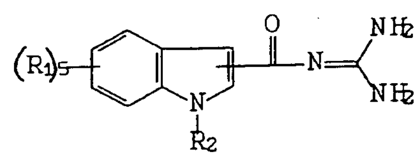
(54) Indoloylguanidine derivatives as inhibitors of sodium-hydrogen exchange.

(57) Novel indoloylguanidine derivatives of the following formula (I), and pharmaceutically acceptable salts thereof, inhibit the Na^+/H^+ exchanger activity and are therefore useful in the treatment and prevention of disease caused by increased Na^+/H^+ exchanger activity.



(1)

wherein

each R_1, which may be the same or different, is independently selected from hydrogen, an alkyl group, a substituted alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a halogen, a nitro group, an acyl group, a carboxyl group, an alkoxycarbonyl group, an aromatic group, and a group of formula : $-OR_3$, $-NR_6R_7$, $-SO_2NR_6R_7$ or $-S(O)_nR_{40}$;

R_2 is a hydrogen atom, an alkyl group, a substituted alkyl group, a cycloalkyl group, a hydroxy group, an alkoxy group or a group of formula $-CH_2R_{20}$;

R_3 is hydrogen, an alkyl group, a substituted alkyl group, a cycloalkyl group or a group shown by formula :

$-CH_2R_{30}$, wherein R_{30} represents an alkenyl group or an alkynyl group ;

each of R_6 and R_7, which may be the same or different, is independently selected from hydrogen, an alkyl group, a substituted alkyl group, a cycloalkyl group, an acyl group and a group of formula :

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$-CH_2R_{60}$, wherein R_{60} represents an alkenyl group or an alkynyl group ; or R_6 and R_7, together with the nitrogen atom to which they are attached, form a saturated 5- to 7- membered cyclic amino group which optionally includes at least one other hetero atom in the ring ;

R_{40} is an alkyl group or a substituted alkyl group ;

n is 0, 1 or 2 ;

and,

R_{20} is an alkenyl group or an alkynyl group ;

and wherein the substituents R_1 and the guanidinocarbonyl group $-C(=O)-N=C(NH_2)_2$ are each, independently, attached to any one of the 5- and 6- membered rings of the indole nucleus ;
or a pharmaceutically acceptable acid addition salt thereof.

The present invention relates to novel indoloylguanidine derivatives. The present invention also relates to sodium/proton (Na^+/H^+) exchanger inhibitors comprising the indoloylguanidine derivatives as the active component which are useful for the treatment and prevention of diseases caused by increased sodium/proton (Na^+/H^+) exchanger activity.

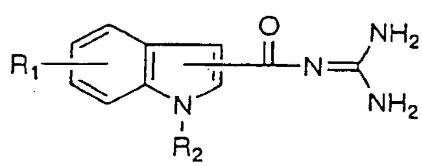
Certain polycyclic aroylguanidine derivatives are known as those having polycondensed rings, for example, a naphthalene, 9,10-dihydroanthracene, benzofuran, 2,3-dihydrobenzofuran, benzothiophene, benzothiazole, methylenedioxybenzene, pyridothiophene, pyrimidothiophene, quinoline, 1,6-naphthylidine, 1,8-naphthylidine, 3,4-dihydrobenzopyran, 3,4-dihydroquinazolin-4-one, 1,2,3,4-tetrahydroquinazolin-2-one, quinoxaline, 5,6,7,8-tetrahydroquinoxaline, benzoazepine, benzotriazepine, benzimidazolothiazine, benzopyranopyran or benzocarbazole ring. As one of the aroylguanidine derivatives having indole rings there is known 1-guanidino-carbonyltryptophane but this compound is merely registered in Chemical Abstracts under Registered No. 18322-34-4, without any reference to its source.

Turning to some monocyclic aroylguanidine derivatives, pyrazinoylguanidine derivatives represented by, e.g., Amiloride, are known to exhibit the sodium/proton CNa^+/H^+) exchanger inhibition activity and anti-arrhythmic activity, cf., J. Membrane Biol., Vol. 105, 1 (1988); and Circulation, Vol. 79, 1257 (1989). Recent reports also reveal that benzoylguanidine derivatives possess the sodium/proton (Na^+/H^+) exchanger inhibition and anti-arrhythmic activities, cf., J. Mol. Cell. Cardiol., Vol. 24, Supple. I, S. 92 (1992); ibid., Vol. 24, Suppl. I, S. 117 (1992); and Japanese Patent KOKAI Nos. 3-106858 and 5-339228.

An object of the present invention is to provide novel indoloylguanidine derivatives which inhibit the sodium/proton (Na^+/H^+) exchanger activity and are therefore useful for the treatment and prevention of diseases caused by increased sodium/proton (Na^+/H^+) exchanger activity, for example, hypertension, arrhythmia, angina pectoris, cardiac hypertrophy, organ disorders associated with ischemic reperfusion such as cardiac ischemic reperfusion injury, disorders induced by surgical treatment such as organ transplantation or percutaneous transluminal coronary angioplasty (PTCA), cerebro-ischemic disorders such as disorders associated with cerebral infarction, disorders caused after cerebral apoplexy as sequelae, or cerebral edema; or diseases caused by excessive cell proliferation such as proliferation of fibroblast, proliferation of smooth muscle cells or proliferation of mesangium cells, which diseases are, e.g., atherosclerosis, pulmonary fibrosis, hepatic fibrosis, renal fibrosis, glomerular nephrosclerosis, organ hypertrophy, prostatic hypertrophy, diabetic complications or recurrent stricture after PTCA.

Another object of the present invention is to provide compositions comprising the indoloylguanidine derivatives as the active component which inhibit the sodium/proton (Na^+/H^+) exchanger activity and are useful for the prevention and treatment of diseases caused by abnormal sodium/proton (Na^+/H^+) exchanger activity.

The present invention relates to indoloylguanidine derivatives represented by the following formula (1):



(1)

wherein:

R_1 represents one or more, the same or different substituent(s), which comprises a hydrogen atom, an alkyl group, a substituted alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a halogen atom, nitro group, an acyl group, carboxyl group, an alkoxycarbonyl group, an aromatic group, and a group shown by formula: $-OR_3$, $-NR_6R_7$, $-SO_2NR_6R_7$ or $-S(O)_nR_{40}$;

R_2 represents a hydrogen atom, an alkyl group, a substituted alkyl group, a cycloalkyl group, hydroxy group, an alkoxy group or a group shown by formula: $-CH_2R_{20}$;

R_3 represents a hydrogen atom, an alkyl group, a substituted alkyl group, a cycloalkyl group or a group shown by formula: $-CH_2R_{30}$, wherein R_{30} represents an alkenyl group or an alkynyl group;

each of R_6 and R_7 independently represents a hydrogen atom, an alkyl group, a substituted alkyl group, a cycloalkyl group, an acyl group or a group shown by formula: $-CH_2R_{60}$, wherein R_{60} represents an alkenyl

group or an alkynyl group; or R_6 and R_7 are combined together to form a saturated 5- to 7-membered cyclic amino group which may contain other hetero atom(s) in the ring thereof;

R_{40} represents an alkyl group or a substituted alkyl group;

n represents 0, 1 or 2;

and,

R_{20} represents an alkenyl group or an alkynyl group;

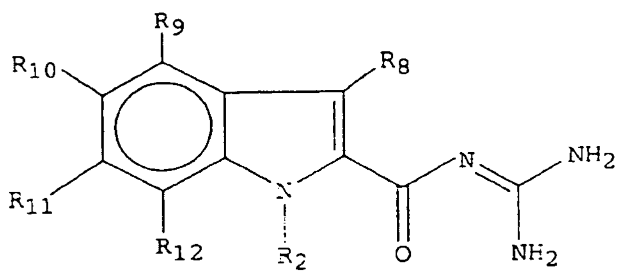
provided that R_1 and the guanidinocarbonyl group may be substituted at any one of the 5- and 6-membered rings of the indole nucleus;

and,

pharmaceutically acceptable acid addition salts thereof.

Typically the guanidinocarbonyl group is bonded at one of positions 2 and 3 of the indole nucleus (i.e. in the 5-membered ring) and the groups R_1 are bonded at the other of positions 2 and 3 and at each of positions 5, 6, 7 and 8 of the indole nucleus (i.e. in the 6-membered ring).

Among the indoloylguanidine derivatives of formula (1), the compounds represented by formula (2) are particularly preferred:



(2)

wherein:

each of R_8, R_9, R_{10}, R_{11} and R_{12} independently represents a hydrogen atom, an alkyl group, a substituted alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a halogen atom, nitro group, an acyl group, carboxyl group, an alkoxycarbonyl group, an aromatic group, or a group shown by formula: $-OR_3$, $-NR_6R_7$, $-SO_2NR_6R_7$ or $-S(O)_nR_{40}$;

R_2 represents a hydrogen atom, an alkyl group, a substituted alkyl group, a cycloalkyl group, hydroxy group, an alkoxy group or a group shown by formula:

$$-CH_2R_{20};$$

R_3 represents a hydrogen atom, an alkyl group, a substituted alkyl group, a cycloalkyl group or a group shown by formula: $-CH_2R_{30}$, wherein R_{30} represents an alkenyl group or an alkynyl group;

each of R_6 and R_7 independently represents a hydrogen atom, an alkyl group, a substituted alkyl group, a cycloalkyl group, an acyl group or a group shown by formula: $-CH_2R_{60}$, wherein R_{60} represents an alkenyl group or an alkynyl group; or R_6 and R_7 are combined together to form a saturated 5- to 7-membered cyclic amino group which may contain other hetero atom(s) in the ring thereof;

R_{40} represents an alkyl group or a substituted alkyl group;

n represents 0, 1 or 2; and,

R_{20} represents an alkenyl group or an alkynyl group;

and,

a pharmaceutically acceptable acid addition salt thereof.

The respective groups in the indoloylguanidine derivatives of the present invention are described below in detail.

The alkyl group refers to a straight or branched alkyl group having carbon atoms of 8 or less, for example, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl, heptyl and octyl.

The alkenyl group refers to an alkenyl group having carbon atoms up to 6, e.g., vinyl, allyl, isopropenyl, 1-propenyl, butenyl, pentenyl and hexenyl.

The alkynyl group refers to an alkynyl group having 2 to 6 carbon atoms, e.g., ethynyl, propargyl, butynyl

and pentynyl.

The cycloalkyl group refers to a cycloalkyl group having 3 to 7 carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Typical examples of the halogen atom include fluorine, chlorine and bromine.

The acyl group refers to a straight or branched alkanoyl group having carbon atoms up to 8, e.g., acetyl, propanoyl and 2-methylpropanoyl; an arylalkanoyl group having carbon atoms up to 10, e.g., phenylacetyl and phenylpropanoyl; and an aroyl group having carbon atoms of 11 or less, e.g., benzoyl, 1-naphthoyl and 2-naphthoyl.

The alkoxycarbonyl group refers to a straight or branched alkoxycarbonyl group having carbon atoms up to 6, e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and 2-propoxycarbonyl.

The aromatic group refers to an aryl or heteroaryl group which may have a substituent. Examples of the aryl group are those having carbon atoms up to 10, e.g., phenyl, tolyl or naphthyl, and examples of the heteroaryl group are a 5- or 6-membered aromatic group containing 1 to 4 nitrogen atoms or a 5- or 6-membered aromatic ring containing 1 to 2 nitrogen atoms and one oxygen atom or one sulfur atom, e.g., 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 1-, 3- or 4-oxazolyl, and 3-, 4- or 5-isoxazolyl.

Examples of the substituent in the substituted aryl or heteroaryl group include hydroxy group, an alkoxy group, a halogen atom, nitro and a group shown by formula: $-NR_6R_7$.

The alkoxy group refers to a straight or branched alkoxy group having carbon atoms up to 6, e.g., methoxy, ethoxy, isopropoxy and tert-butoxy.

As the saturated 5- to 7-membered cyclic amino group which is formed by combining R_6 and R_7 together and may contain other hetero atoms therein, there are, for example, a 5- to 7-membered cyclic group containing 1 to 3 nitrogen atoms and a 5- to 7-membered cyclic group containing one nitrogen atom and one oxygen atom. Specific examples of such cyclic amino group include 1-pyrrolidinyl, piperidino, 1-piperazinyl, morpholino and 4-methylmorpholino.

Examples of the substituent in the substituted alkyl group include a cycloalkyl group, a halogen atom, hydroxy, an alkoxy group, cyano, carboxyl, an alkoxycarbonyl group, an acyl group, an aromatic group, or a group shown by formula: $-CONR_4R_5$ or $-NR_6R_7$, wherein each of R_4 and R_5 independently represents hydrogen atom or an alkyl group, or R_4 and R_5 are combined together to form a saturated 5- to 7-membered cyclic amino group which may contain other hetero atoms in the ring. Particularly where R_1, R_2 and R_3 represent a substituted alkyl group, examples of the substituent include a cycloalkyl group, a halogen atom, hydroxy, an alkoxy group, carboxyl, an alkoxycarbonyl group, an acyl group, an aromatic group or a group shown by formula: $-CONR_4R_5$ or $-NR_6R_7$. Where R_6 and R_7 represent a substituted alkyl group, examples of the substituent include a cycloalkyl group, hydroxy, an alkoxy group, carboxyl, an alkoxycarbonyl group, an acyl group, an aryl group or a group shown by formula: $-CONR_4R_5$ or $-NR_4R_5$. As the alkyl moiety in the substituted alkyl group, the same examples as those for the alkyl group described above are given.

As such a substituted alkyl group, there are, for example, an alkyl group having 1 to 5 carbon atoms which is substituted with a cycloalkyl having 3 to 6 carbon atoms, a polyhaloalkyl group having 1 to 5 carbon atoms, a hydroxyalkyl group having 1 to 6 carbon atoms, an alkoxyalkyl group having 2 to 6 carbon atoms, a cyanoalkyl group having 2 to 6 carbon atoms, a carboxyalkyl group having 2 to 6 carbon atoms, an alkoxycarbonylalkyl group having 3 to 8 carbon atoms, an alkanoylalkyl group having 3 to 8 carbon atoms, an aroylalkyl group having carbon atoms up to 16, a phenyl- or naphthyl-C_1 to C_5 alkyl group which may be substituted, a carbamoyl-C_1 to C_3 alkyl group in which the nitrogen atom may be substituted with one or two C_1 to C_3 alkyl, an amino-C_1 to C_5 alkyl group in which the nitrogen atom may be substituted with one or two C_1 to C_3 alkyl or C_7 to C_{11} aralkyl, and a saturated 5- to 7-membered cyclic amino-C_1 to C_3 alkyl group.

Representative examples of the substituted alkyl group include:

in the case of R_1: a polyhaloalkyl group having 1 to 3 carbon atoms such as trifluoromethyl, trifluoroethyl or trichloromethyl; a hydroxyalkyl group having 1 to 6 carbon atoms such as hydroxymethyl, hydroxyethyl or 1-hydroxyethyl; and an aminoalkyl group having 1 to 5 carbon atoms such as aminomethyl, aminoethyl or 1-aminoethyl;

in the case of R_2: a hydroxyalkyl group having 1 to 6 carbon atoms such as hydroxyethyl, hydroxypropyl, hydroxybutyl, 2-hydroxypropyl or 3,4-dihydroxybutyl; an alkoxyalkyl group having 1 to 6 carbon atoms such as methoxyethyl, ethoxyethyl or methoxypropyl; a carboxyalkyl group having 2 to 6 carbon atoms such as carboxyethyl or carboxypropyl; an alkoxycarbonylalkyl group having 3 to 7 carbon atoms such as methoxycarbonylmethyl, ethoxycarbonylmethyl or methoxycarbonylethyl; a phenyl- or naphthyl-C_1 to C_5 alkyl group (wherein a phenyl or naphthyl group may be substituted with a substituent, e.g., a C_1 to C_3 alkyl group, a halogen atom, nitro, amino, hydroxy or a C_1 to C_3 alkoxy group) such as benzyl, phenylethyl, phenylpropyl, phenylbutyl or, 1- or 2-naphthylmethyl; a carbamoyl-C_1 to C_3 alkyl group in which the nitrogen atom may be substituted with one or two C_1 to C_3 alkyl groups, such as carbamoylmethyl, carbamoylethyl or dimethylcarbamoylmethyl; or,

an amino-C_1 to C_5 alkyl group in which the nitrogen atom may be substituted with one or two C_1 to C_3 alkyl, such as aminoethyl, aminopropyl, dimethylaminoethyl or diethylaminoethyl;

in the case of R_3 and R_{40}: a hydroxyalkyl group having 1 to 6 carbon atoms such as hydroxyethyl, hydroxypropyl, 2-hydroxypropyl, hydroxybutyl or 2,3-dihydroxybutyl; a carboxyalkyl group having 2 to 6 carbon atoms such as carboxymethyl or carboxyethyl; a phenyl-C_1 to C_5 alkyl group such as benzyl, phenylethyl or phenylpropyl; a carbamoyl-C_1 to C_3 alkyl group such as carbamoylmethyl or carbamoylethyl; an amino-C_1 to C_5 alkyl group containing one or two nitrogen atoms in which the nitrogen atom may be substituted with one or two C_1 to C_3 alkyl or C_7 to C_{11} aralkyl groups, such as aminoethyl, aminopropyl, dimethylaminoethyl, dimethylaminopropyl or benzylmethyl-aminoethyl; or a saturated 5- to 7-membered cyclic amino-C_1 to C_3 alkyl group such as 1-pyrrolidinyl-ethyl or piperidinoethyl; and,

in the case of R_6 and R_7: a phenyl-C_1 to C_5 alkyl group such as phenylethyl.

Examples of the saturated 5- to 7-membered cyclic amino group which is formed by combining R_4 and R_5 together and may contain other hetero atoms in the ring thereof include the same groups as exemplified for the aforesaid cyclic amino group formed by R_6 and R_7.

Examples of the group shown by formula: -$S(O)_nR_{40}$ include an alkylsulfonyl group having carbon atoms up to 8, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl or isopropylsulfonyl; and the corresponding alkylsulfinyl and alkylthio groups.

In the indoloylguanidine derivatives of formula (1), the following compounds are more preferred.

1. The indoloylguanidine derivatives of formula (1) wherein:

R_1 represents a hydrogen atom, an alkyl group, a substituted alkyl group, an alkenyl group, a cycloalkyl group, a halogen atom, nitro group, an alkanoyl group, carboxyl group, an aryl group, an alkylsulfonyl group, or a group shown by formula: -OR_3 or -NR_6R_7;

R_3 represents hydrogen atom, an alkyl group or a substituted alkyl group;

each of R_6 and R_7 independently represents hydrogen atom, an alkyl group, a substituted alkyl group, an alkanoyl group, an aroyl group or an arylalkyl group; or R_6 and R_7 are combined together to form a saturated 5- to 7-membered cyclic amino group which may contain other hetero atom(s) in the ring thereof.

2. The indoloylguanidine derivatives described in 1. above, wherein:

R_1 represents a hydrogen atom, an alkyl group, a substituted alkyl group wherein the substituent is a hydroxy group or a group shown by -NR_6R_7, a polyhaloalkyl group, an alkenyl group, a cycloalkyl group, a halogen atom, a nitro group, an alkanoyl group, a carboxyl group, a phenyl group, an alkylsulfonyl group or a group shown by formula -OR_{31} wherein R_{31} represents a hydrogen atom or an alkyl group, or an alkyl group substituted with a hydroxy group, a carboxyl group, a phenyl group, a carbamoyl group, a mono- or di-alkylcarbamoyl group or a group shown by formula: -NR_6R_7.

3. The indoloylguanidine derivatives described in 1. above, wherein:

R_1 represents an alkyl group, a polyhaloalkyl group, an alkenyl group, a halogen atom, a nitro group or a group shown by formula -OR_{32}, wherein R_{32} represents a hydrogen atom or an alkyl group, or an alkyl group substituted with a hydroxy group, a carbamoyl group, or a mono- or di-alkylcarbamoyl group or a group shown by formula: -NR_6R_7.

4. The indoloylguanidine derivatives described in any one of 1 through 3 above, wherein:

R_2 represents a hydrogen atom, an alkyl group, a substituted alkyl group, a hydroxy group or an alkoxy group.

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6. The indoloylguanidine derivatives of formula (2), wherein:

R_8 represents a hydrogen atom, and R_{10} represents a hydrogen atom or a halogen atom.

7. The indoloylguanidine derivatives described in 6. above, wherein:

R_9 represents a hydrogen atom, an alkyl group, a polyhaloalkyl group, a cycloalkyl group, an alkenyl group, a halogen atom, a nitro group, an alkylsulfonyl group or a group shown by formula: -OR_{33} wherein R_{33} represents a hydrogen atom, an alkyl group or an aralkyl group.

8. The indoloylguanidine derivatives described in any one of 6 and 7 above, wherein:

each of R_{11} and R_{12} independently represents a hydrogen atom, an alkyl group, a substituted alkyl group wherein the substituent is a hydroxy group or a group shown by -NR_6R_7, a polyhaloalkyl group, an alkenyl group, a cycloalkyl group, a halogen atom, a nitro group, or a group shown by formula: -OR_3 or -NR_6R_7.

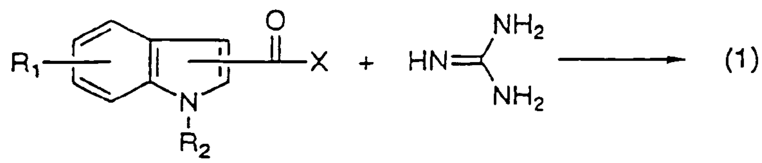
9. The indoloylguanidine derivatives described in any one of 6, 7 and 8 above, wherein:

R_2 represents a hydrogen atom, an alkyl group, a substituted alkyl group, a hydroxy group or an alkoxy group.

The compounds of the present invention represented by the formula (1) above can be prepared by the fol-

lowing processes.

(a)The compounds (1) of the present invention can be obtained by reacting reactive derivatives of indolecarboxylic acid shown by formula (3) with guanidine in an inert solvent.



(3)

wherein X is a leaving group which can be readily replaced by a nucleophilic reagent and, R_1 and R_2 have the same significances as described above.

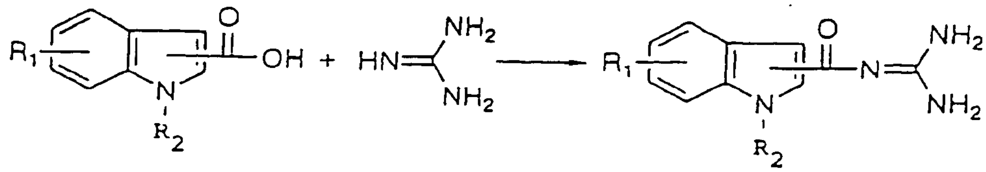
In this reaction, where the indolecarboxylic acid derivatives (3) contain reactive groups such as hydroxy or amino, these groups are previously protected by their protective groups. These protective groups are removed after the reaction is completed. The desired indoloylguanidine derivatives (1) can thus be prepared.

As the reactive derivatives of the carboxylic acid, there are acid halides, acid anhydrides (including mixed acid anhydrides) and ester derivatives. Specific examples are acid chlorides and acid bromides as the acid halides; as the mixed acid anhydrides, there are mixed acid anhydrides with alkyloxy chloride type such as ethyloxycarbonyl chloride or isobutyloxycarbonyl chloride and those with α-polyalkyl-substituted carboxylate type such as diethylacetyl chloride or trimethylacetyl chloride; as the ester derivatives there are activated esters such as p-nitrophenyl esters, N-hydroxysuccinimide esters or pentafluorophenyl esters, and ordinary esters such as methyl esters or ethyl esters. These reactive derivatives of the carboxylic acids can be readily obtained from the corresponding carboxylic acids in a conventional manner.

In the case of performing the reaction between the acid halides or the acid anhydrides (including the mixed acid anhydrides) and guanidine, the reaction can be carried out in a solvent under cooling or at room temperature, in the presence of a base or an excess of guanidine. Inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate or sodium hydrogencarbonate, or organic bases such as triethylamine or pyridine may be used as the base. Examples of the solvent include aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as tetrahydrofuran or 1,4-dioxane, halogenated hydrocarbons such as dichloromethane, chloroform or 1,2-dichloroethane, amides such as dimethylformamide or dimethylacetamide, basic solvents such as pyridine, or a mixture of these solvents.

Where the ester derivatives are reacted, the reaction is carried out in a solvent usually at a elevated temperature, in the presence of an equimolar amount of or an excess of guanidine. In the case of using the activated esters, the reaction is performed preferably in an ethers such as tetrahydrofuran, 1,2-dimethoxyethane or 1,4-dioxane, an ester type solvent such as ethyl acetate, dimethylformamide or a solvent mixture thereof. In the case of using other esters, it is preferred to perform the reaction in an alcohol type solvent such as methanol, ethanol or isopropanol, an ether type solvent such as tetrahydrofuran, 1,2-dimethoxyethane or 1,4-dioxane, dimethylformamide or a solvent mixture thereof. After removal of the solvent, if necessary and desired, the reaction system may be heated at about 130°C for a short period of time.

(b)The compounds (1) of the present invention can be obtained by reacting indolecarboxylic acids shown by formula (4) with guanidine in an inert solvent at room temperature or with heating, preferably in the presence of a condensing agent.



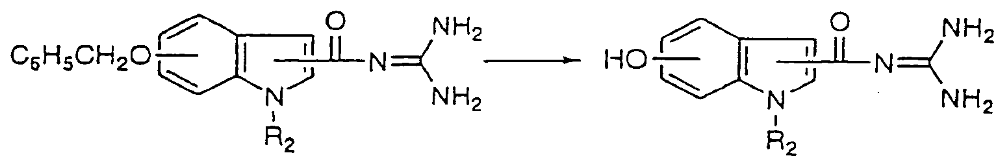
(4) (1)

wherein R_1 and R_2 have the same significances as described above.

In this reaction, where the indolecarboxylic acid derivatives (4) contain reactive groups such as hydroxy or amino, these groups are previously protected by their protective groups. These protective groups are removed after the reaction is completed. The desired indoloylguanidine derivatives (1) can thus be prepared.

The reaction is carried out in a solvent, e.g., aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as tetrahydrofuran or 1,4-dioxane, halogenated hydrocarbons such as dichloromethane, chloroform or 1,2-dichloroethane, amides such as dimethylformamide or dimethylacetamide, basic solvents such as pyridine, or a mixture of these solvents, in the presence of a condensing agent, e.g., dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIPC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC), benzotriazol-1-yl-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), diphenylphosphonylazide (DPPA) or N,N-carbonyldiimidazole, cf., Angew. Chem. Int. Ed. Engl., Vol. 1, 351 (1962), and, if desired, in the presence of an additive such as N-hydroxysuccinimide (HONSu), 1-hydroxybenzotriazole (HOBt), 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HOObt), etc.

(c) The compounds (1a) of the present invention can be obtained by debenzylation of benzyloxyindoloylguanidine derivatives shown by general formula (5).

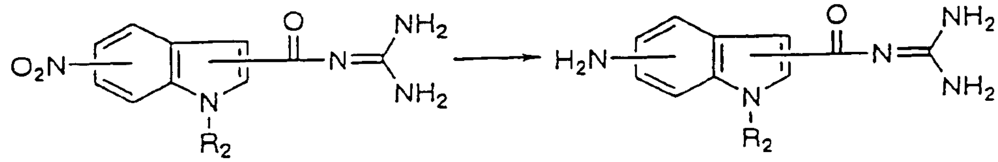


(5) (1a)

wherein R_2 has the same significance as described hereinabove.

The debenzylation is carried out in a manner similar to the processes described in publications, such as catalytic hydrogenation using a palladium/carbon catalyst, cf., J. Chem. Soc., 1953, 4058 or decomposition under acidic conditions using hydrochloric acid/acetic acid, cf., J. Amer. Chem. Soc., Vol. 73, 5765 (1951).

(d) The compounds (1b) of the present invention can be obtained by reducing nitroindoloylguanidine derivatives represented by formula (6).



(6) (1b)

wherein R_2 has the same significance as described hereinabove.

As the reducing conditions applicable, there are conditions, e.g., reduction under acidic conditions using zinc, iron, tin or tin (II) chloride, cf., Ann., 641, 81 (1961), J. Amer. Chem. Soc., Vol. 66, 1781 (1944); reducing using sulfides such as sodium dithionite ($Na_2S_2O_4$), cf., J. Amer. Chem. Soc., Vol. 72, 1361 (1950); catalytic hydrogenation using catalysts such as palladium/carbon, cf., Synth. Commun., 147(1971) or Raney nickel, cf., Org. Synth., IV, 226 (1963).

As the protective groups for the hydroxy, amino or carboxyl group reactive with the reaction in the process (a) or (b) described hereinabove, there may be used protective groups conventionally used in the field of organic synthesis chemistry. Introduction and removal of these protective groups can be made in a conventional manner, e.g., Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

Examples of the protective group for the hydroxy group include methoxymethyl and tetrahydro-pyranyl. Examples of the protective group for the amino group include tert-butyloxycarbonyl and the like. These protective groups for the hydroxy group can be removed by conducting the reaction in a solvent such as hydrated methanol, hydrated ethanol or hydrated tetrahydrofuran in the presence of an acid, e.g., hydrochloric acid, sulfuric acid or acetic acid. The amino protective groups can be removed by performing the reaction in a solvent such as hydrated tetrahydrofuran, methylene chloride, chloroform or hydrated methanol, in the presence of an acid, e.g., hydrochloric acid or trifluoroacetic acid.

For protecting the carboxyl group, the protection is effected in the form of tert-butyl esters, ortho-esters or acid amides. Such protective groups are removed, in the case of the tert-butyl esters, e.g., by performing the reaction in a hydrated solvent in the presence of hydrochloric acid; in the case of the orthoesters, the protective groups are removed, e.g., by treating the protected compounds with an acid in a solvent such as hydrated methanol, hydrated tetrahydrofuran or hydrated 1,2-dimethoxyethane and then with an alkali such as sodium hydroxide. In the case of the acid amides, the protective groups are removed, e.g., by conducting the reaction in a solvent such as water, hydrated methanol or hydrated tetrahydrofuran in the presence of an acid such as hydrochloric acid or sulfuric acid.

The indolecarboxylic acids which are the starting compounds in the processes (a) and (b) described hereinabove are commercially available. Examples of such commercially available indolecarboxylic acids are indole-5-carboxylic acid, 5-chloro-2-indole carboxylic acid, indole-3-carboxylic acid, indole-2 carboxylic acid, indole-4-carboxylic acid, 5-methoxy-2-indolecarboxylic acid. Alternatively, the indolecarboxylic acids may be prepared by known methods.

According to, e.g., the method of Reissert (Reissert's indole synthesis), there can be prepared 4-chloro-2-indolecarboxylic acid, cf., J. Chem. Soc., 1955, 3490; 6-n-amyl-2-indolecarboxylic acid, cf., J. Amer. Chem. Soc., Vol. 75, 4921 (1953); 7-indole-carboxylic acid, cf., J. Amer. Chem. Soc., Vol. 77, 5700 (1955);, 5-cyano-2-indolecarboxylic acid, cf., J. Org. Chem., Vol. 18, 354 (1953); 6-cyano-2-indolecarboxylic acid, cf., J. Chem. Soc., 1924, 2285; 6-benzyloxy-2-indolecarboxylic acid, cf., J. Chem. Soc., 1937, 1726 and the like.

The method of Fischer (Fischer's indole synthesis) gives nitro-2-indolecarboxylic acids in J. Amer. Chem. Soc., Vol. 80, 4621 (1958), 7-chloro-2-indolecarboxylic acid in J. Chem. Soc., 1955, 3499, 4-trifluoromethyl-2-indolecarboxylic acid in J. Amer. Chem. Soc., Vol. 79, 1745 (1957) and the like.

The 2-indolecarboxylic acids may also be prepared by known methods using benzaldehyde derivatives as the starting compounds, see, e.g., Tetrahedron, Vol. 42, 3259 (1986).

The 4-indolecarboxylic acids, 5-indolecarboxylic acids and 6-indolecarboxylic acids can be prepared based on the methods described in, e.g., J. Chem. Tech. Biotechnol., Vol. 36, 562 (1986), Tetrahedron Letters, Vol. 27, 1653 (1986), etc.

The 1-hydroxyindolecarboxylic acids can be prepared based on the method described in Chem. Ber., Vol. 56, 1024 (1923).

The compounds of formula (1) prepared as described above are illustratively given below.

1-methyl-2-indoloylguanidine
1-methyl-3-indoloylguanidine
1-methyl-4-indoloylguanidine
1-methyl-5-indoloylguanidine
1-methyl-6-indoloylguanidine
4-chloro-1-methyl-2-indoloylguanidine
5-chloro-1-methyl-2-indoloylguanidine
6-chloro-1-methyl-2-indoloylguanidine
7-chloro-1-methyl-2-indoloylguanidine
5-chloro-2-indoloylguanidine
1,4-dimethyl-2-indoloylguanidine
1,5-dimethyl-2-indoloylguanidine
1,6-dimethyl-2-indoloylguanidine
1,7-dimethyl-2-indoloylguanidine
4-methoxy-1-methyl-2-indoloylguanidine
5-methoxy-1-methyl-2-indoloylguanidine
6-methoxy-1-methyl-2-indoloylguanidine
7-methoxy-1-methyl-2-indoloylguanidine
1-methyl-4-nitro-2-indoloylguanidine
1-methyl-5-nitro-2-indoloylguanidine
1-methyl-6-nitro-2-indoloylguanidine
1-methyl-7-nitro-2-indoloylguanidine
4-amino-1-methyl-2-indoloylguanidine
5-amino-1-methyl-2-indoloylguanidine
6-amino-1-methyl-2-indoloylguanidine
7-amino-1-methyl-2-indoloylguanidine
1-benzyl-2-indoloylguanidine
1-benzyl-3-indoloylguanidine
1-benzyl-5-indoloylguanidine
1-isopropyl-2-indoloylguanidine
1-isopropyl-3-indoloylguanidine
1-isopropyl-5-indoloylguanidine
2-indoloylguanidine
3-indoloylguanidine
5-indoloylguanidine
4-hydroxy-1-methyl-2-indoloylguanidine
5-hydroxy-1-methyl-2-indoloylguanidine
6-hydroxy-1-methyl-2-indoloylguanidine
7-hydroxy-1-methyl-2-indoloylguanidine
1-(3-dimethylaminopropyl)-4-trifluoromethyl-2-indoloylguanidine
1-(3-diethylaminopropyl)-4-trifluoromethyl-2-indoloylguanidine
1-[3-(N-pyrrolidinyl)propyl]-4-trifluoromethyl-2-indoloylguanidine
6-(3-aminopropoxy)-1-methyl-4-trifluoromethyl-2-indoloylguanidine
6-(3-dimethylaminopropoxy)-1-methyl-4-trifluoromethyl-2-indoloylguanidine
6-(3-diethylaminopropoxy)-1-methyl-4-trifluoromethyl-2-indoloylguanidine
6-(2-aminoethoxy)-1-methyl-4-trifluoromethyl-2-indoloylguanidine
6-(2-dimethylaminoethoxy)-1-methyl-4-trifluoromethyl-2-indoloylguanidine
6-(2-diethylaminoethoxy)-1-methyl-4-trifluoromethyl-2-indoloylguanidine
1-methyl-6-[3-(N-pyrrolidinyl)propoxy]-4-trifluoromethyl-2-indoloylguanidine
1-methyl-6-[2-(N-pyrrolidinyl)ethoxy]-4-trifluoromethyl-2-indoloylguanidine
1-(3-dimethylaminopropyl)-4-methoxy-2-indoloylguanidine
1-(3-diethylaminopropyl)-4-methoxy-2-indoloylguanidine
1-(3-aminopropyl)-4-methoxy-2-indoloyl-guanidine
4-methoxy-1-[3-(N-pyrrolidinyl)propoyl]-2-indoloylguanidine
6-(3-aminopropoxy)-4-methoxy-1-methyl-2-indoloylguanidine
6-(3-dimethylaminopropoxy)-4-methoxy-1-methyl-2-indoloylguanidine
6-(3-diethylaminopropoxy)-4-methoxy-1-methyl-2-indoloylguanidine

6-(2-aminoethoxy)-4-methoxy-1-methyl-2-indoloylguanidine
6-(2-dimethylaminoethoxy)-4-methoxy-1-methyl-2-indoloylguanidine
6-(2-diethylaminoethoxy)-4-methoxy-1-methyl-2-indoloylguanidine
4-methoxy-1-methyl-6-[3-(N-pyrrolidinyl)-propoxy]-2-indoloylguanidine
4-methoxy-1-methyl-6-[2-(N-pyrrolidinyl)-ethoxy]-2-indoloylguanidine
7-(3-aminopropoxy)-4-methoxy-1-methyl-2-indoloylguanidine
7-(3-dimethylaminopropoxy)-4-methoxy-1-methyl-2-indoloylguanidine
7-(3-diethylaminopropoxy)-4-methoxy-1-methyl-2-indoloylguanidine
4-methoxy-1-methyl-7-[3-(N-pyrrolidinyl)-propoxy]-2-indoloylguanidine
1-(3-dimethylaminopropyl)-4-isopropoxy-2-indoloylguanidine
1-(3-diethylaminopropyl)-4-isopropoxy-2-indoloylguanidine
1-(3-aminopropyl)-4-isopropoxy-2-indoloylguanidine
4-isopropoxy-1-[3-(N-pyrrolidinyl)propyl]-2-indoloylguanidine
6-(3-aminopropoxy)-4-isopropoxy-1-methyl-2-indoloylguanidine
6-(3-dimethylaminopropoxy)-4-isopropoxy-1-methyl-2-indoloylguanidine
6-(3-diethylaminopropoxy)-4-isopropoxy-1-methyl-2-indoloylguanidine
6-(2-aminoethoxy)-4-isopropoxy-1-methyl-2-indoloylguanidine
6-(2-dimethylaminoethoxy)-4-isopropoxy-1-methyl-2-indoloylguanidine
6-(2-diethylaminoethoxy)-4-isopropoxy-1-methyl-2-indoloylguanidine
4-isopropoxy-1-methyl-6-[3-(N-pyrrolidinyl)-propoxy]-2-indoloylguanidine
4-isopropoxy-1-methyl-6-[2-(N-pyrrolidinyl)-ethoxy]-2-indoloylguanidine
7-(3-aminopropoxy)-4-isopropoxy-1-methyl-2-indoloylguanidine
7-(3-dimethylaminopropoxy)-4-isopropoxy-1-methyl-2-indoloylguanidine
7-(3-diethylaminopropoxy)-4-isopropoxy-1-methyl-2-indoloylguanidine
4-isopropoxy-1-methyl-7-[3-(N-pyrrolidinyl)-propoxy]-2-indoloylguanidine
1-(3-aminopropyl)-4-methyl-2-indoloylguanidine
1-(3-dimethylaminopropyl)-4-methyl-2-indoloylguanidine
1-(3-diethylaminopropyl)-4-methyl-2-indoloylguanidine
4-methyl-1-[3-(N-pyrrolidinyl)propyl]-2-indoloylguanidine
6-(3-aminopropoxy)-1,4-dimethyl-2-indoloylguanidine
1,4-dimethyl-6-(3-dimethylaminopropoxy)-2-indoloylguanidine
6-(3-diethylaminopropoxy)-1,4-dimethyl-2-indoloylguanidine
1,4-dimethyl-6-(2-diethylaminoethoxy)-2-indoloylguanidine
6-(2-diethylaminoethoxy)-1,4-dimethyl-2-indoloylguanidine
6-(2-aminoethoxy)-1,4-dimethyl-2-indoloylguanidine
1,4-dimethyl-6-[3-(N-pyrrolidinyl)propoxy]-2-indoloylguanidine
1,4-dimethyl-6-[2-N-pyrrolidinyl)ethoxy]-2-indoloylguanidine
7-(3-aminopropoxy)-1,4-dimethyl-2-indoloylguanidine
1,4-dimethyl-7-(3-dimethylaminopropoxy)-2-indoloylguanidine
7-(3-diethylaminopropoxy)-1,4-dimethyl-2-indoloylguanidine
1,4-dimethyl-7-[3-(N-pyrrolidinyl)propoxy]-2-indoloylguanidine
4-ter-butyl-1-methyl-2-indoloylguanidine
1-(3-aminopropyl)-4-tert-butyl-2-indoloylguanidine
4-tert-butyl-1-(3-dimethylaminopropyl)-2-indoloylguanidine
4-tert-butyl-1-(3-diethylaminopropyl)-2-indoloylguanidine
4-tert-butyl-1-[3-(N-pyrrolidinyl)propyl]-2-indoloylguanidine
6-(3-dimethylaminopropoxy)-1-methyl-2-indoloylguanidine
6-(3-diethylaminopropoxy)-1-methyl-2-indoloylguanidine
6-(2-aminoethoxy)-1-methyl-2-indoloylguanidine
6-(2-dimethylaminoethoxy)-1-methyl-2-indoloylguanidine
6-(2-diethylaminoethoxy)-1-methyl-2-indoloylguanidine
1-methyl-6-[3-(N-pyrrolidinyl)propoxy]-2-indoloylguanidine
1-methyl-6-[2-(N-pyrrolidinyl)ethoxy]-2-indoloylguanidine
7-(3-dimethylaminopropoxy)-1-methyl-2-indoloylguanidine
7-(3-diethylaminopropoxy)-1-methyl-2-indoloylguanidine
1-methyl-7-[3-(N-pyrrolidinyl)propoxy]-2-indoloylguanidine

The compounds represented by formula (1) may be converted into acid addition salts with pharmaceutically acceptable inorganic acids or organic acids, if necessary and desired. Examples of such acid addition

salts are salts with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid; salts with organic acids such as formic acid, acetic acid, fumaric acid, maleic acid, oxalic acid, citric acid, malic acid, tartaric acid, aspartic acid or glutamic acid; salts with sulfonic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, hydroxybenzenesulfonic acid, dihydroxybenzenesulfonic acid, etc.

The compounds of the present invention inhibit the sodium/proton (Na^+/H^+) exchanger system and are thus useful for the treatment and prevention of diseases caused by increased sodium/proton (Na^+/H^+) exchanger activity, for example, hypertension, arrhythmia, angina pectoris, cardiac hypertrophy, organ disorders associated with ischemic reperfusion (e.g., myocardial ischemic reperfusion disturbance, disorders caused by surgical treatment (e.g., organ transplantation or PTCA), cerebroischemic disorders (e.g., disorders associated with cerebral infarction, disorders caused after cerebral apoplexy as sequelae or cerebral edema), or diseases (e.g., atherosclerosis, pulmonary fibrosis, hepatic fibrosis, renal fibrosis, glomerular nephrosclerosis, organ hypertrophy, prostatic hypertrophy, diabetic complications or recurrent stricture after PTCA) caused by excessive cell proliferation such as proliferation of fibroblast, proliferation of smooth muscle cells or proliferation of mesangium cells).

The compounds of the present invention can be prepared in the form of pharmaceutical preparations which are suitable for oral or parenteral administration. These pharmaceutical preparations can be administered orally in the form of powders, granules, tablets, capsules, syrup or suspensions; alternatively, parenterally in the form of injections using its solution, emulsion or suspension. The pharmaceutical preparations may also be administered rectally in the form of suppositories.

These pharmaceutical compositions can be prepared by mixing the compound of the present invention as the active ingredient with a conventionally acceptable carrier, a recipient, a binder, a stabilizer and a diluent. In the case of using the compound of the present invention in the form of injection, a pharmaceutically acceptable buffer, a dissolution aid or an isotonic agent may also be incorporated in the composition.

Dosage and time of administration may vary depending upon the disease, condition, age, body weight and mode of administration but the composition is administered in a daily dose of 0.1 to 2000 mg, preferably 1 to 200 mg, for adult at once or by dividing into several times.

The present invention is described below more specifically by referring to Reference Examples, Examples and Experiments but not deemed to be limited thereto.

Reference Example 1

Preparation of 7-chloro-2-indolecarboxylic acid (Fischer's indole synthesis)

a) Preparation of ethyl 2-(2-chlorophenyl)hydrazonopropionate

To a solution of 14.4 g (0.10 mol) of ethyl 2-methylacetacetate in 100 ml of ethanol was added dropwise 50 g of 50% potassium hydroxide aqueous solution at 0°C. After 70 g of ice was added to the solution, a diazonium salt solution prepared by mixing 12.8 g (0.10 mol) of o-chloroaniline, 13.6 g (0.20 mol) of sodium nitrite and 60 g of conc. hydrochloric acid was added to the mixture at once. The reaction mixture was stirred at 0°C for 30 minutes. The precipitates were cellected and dried under reduced pressure to give 9.10 g (37.7%) of the desired ethyl 2-(2-chlorophenyl)hydrazonopropionate.

b) Preparation of ethyl 7-chloro-2-indolecarboxylate

After 8.00 g (33.2 mmol) of ethyl 2-(2-chlorophenyl)hydrazonopropionate obtained above was added to 20 g of polyphosphoric acid, the mixture was gradually heated to 190°C, which was kept for 5 minutes. The reaction mixture was cooled to 60°C and water was then added thereto. The mixture was extracted 3 times with ethyl acetate. The combined extracts were washed with water. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain 3.40 g (45.7%) of the desired ethyl 7-chloro-2-indolecarboxylate.

^1H NMR ($CDCl_3$) δ: 1.40-1.46 (3H, m), 4,43 (2H, dd, J=7.3, 14.2Hz), 7.09 (1H, t, J=7.9Hz), 7.25 (1H, d, J=2.3Hz), 7.32 (1H, dd, J=1.0, 7.6Hz), 7.58-7.61 (1H, m), 9.02 (1H, br-s).

The following compounds were prepared by carrying out the reaction in a manner similar to Reference Example 1.

(1) Ethyl 5-nitro-2-indolecarboxylate:

^1H NMR ($CDCl_3$) δ: 1.42-1.47 (3H, m), 4.45 (2H, dd, J=7.3, 14.2Hz), 7.38 (1H, dd, J=0.7, 2.0Hz), 7.50 (1H, d, J=9.3Hz), 8.21-8.25 (1H, m), 8.69 (1H, d, J=2.0Hz), 9.3 (1H, br-s).

(2) Ethyl 7-nitro-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.42-1.48 (3H, m), 4.43-4.51 (2H, m), 7.25-7.28) (1H, m), 7.37 (1H, d, J=2.3Hz), 8.04-8.08 (1H, m), 8.31 (1H, dd, J=1.0, 7.9Hz), 10.4 (1H, br-s).

(3) Ethyl 4-methoxy-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.38-1.43 (3H, m), 3.96 (3H, s), 4.36-4.44 (2H, m), 6.51 (1H, d, J=7.9Hz), 7.01 (1H, d, J=8.3Hz), 7.22 (1H, d, J=7.9Hz), 7.34-7.35 (1H, m), 8.9 (1H, br-s).

(4) Ethyl 6-methoxy-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.38-1.43 (3H, m), 3.85 (3H, s), 4.39 (2H, dd, J=7.3, 14.2Hz), 6.80-6.84 (2H, m), 7.16-7.17 (1H, m), 7.52-7.56 (1H, m), 8.9 (1H, br-s).

(5) Ethyl 4-nitro-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.44-1.49 (3H, m), 4.43-4.51 (2H, m), 7.41-7.47 (1H, m), 7.77-7.80 (1H, m), 7.92 (1H, dd, J=1.0, 2.3Hz), 8.20 (1H, dd, J=0.7, 7.9Hz), 9.4 (1H, br-s).

(6) Ethyl 6-nitro-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.46 (3H, t, J=7.3Hz), 4.48 (2H, dd, J=7.3, 14.2Hz), 7.29-7.30 (1H, m), 7.78 (1H, d, J=8.9Hz), 8.05 (1H, dd, J=2.0, 8.9Hz), 8.42 (1H, t, J=1.0Hz), 9.6 (1H, br-s).

(7) Ethyl 4-trifluoromethyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.42-1.47 (3H, m), 4.45 (2H, dd, J=6.9, 14.2Hz), 7.35-7.41 (2H, m), 7.46-7.49 (1H, m), 7.62 (1H, d, J=8.3Hz), 9.32 (1H, br-s).

(8) Ethyl 6-trifluoromethyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.41-1.47 (3H, m), 4.41-4.49 (2H, m), 7.26-7.27 (1H, m), 7.36-7.40 (1H, m), 7.73-7.81 (2H, m), 9.26 (1H, br-s).

(9) Ethyl 7-phenyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.28-1.43 (3H, m), 4.41 (2H, dd, J=6.9, 14.2Hz), 7.20-7.26 (1H, m), 7.35-7.57 (6H, m), 7.66-7.70 (2H, m), 9.11 (1H, br-s).

(10) Ethyl 4-acetyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.41-1.47 (3H, m), 2.72 (3H s), 4.40-4.48 (2H, m), 7.38 (1H, dd, J=7.3, 8.2Hz), 7.66 (1H, dd, J=1.0, 8.3Hz), 7.78 (1H, dd, J=1.0, 7.3Hz), 7.99-8.00 (1H, m), 9.42 (1H, br-s).

Reference Example 2

Preparation of 4-methyl-2-indolecarboxylic acid (Reissert's indole synthesis)

a) Preparation of (6-methyl-2-nitrophenyl)pyruvic acid

A solution of 15.1 g (0.10 mol) of 2-methyl-3-nitrotoluene and 14.6 g (0.10 mol) of diethyl oxalate in 10 ml of ethanol was added to a solution of 11.2 g (0.10 mol) of potassium tert-butoxide in 50 ml of ethanol. After stirring at room temperature for 1.5 hour, the reaction mixture was refluxed for 1.5 hour. After 60 ml of water was added to the reaction mixture, the mixture was refluxed for further an hour. After cooling, ice water was poured onto the reaction mixture followed by washing twice with ethyl acetate. The aqueous layer was acidified with conc. hydrochloric acid and then extracted three times with chloroform. The combined extracts were washed with water. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure to give 10.4 g (46.6%) of the desired 6-methyl-2-nitrophenylpyruvic acid.

b) Preparation of 4-methyl-2-indolecarboxylic acid

A 5% aqueous ammonia of 10.4 g (46.6 mmol) of 6-methyl-2-nitrophenylpyruvic acid obtained above was added to a suspension of 96.4 g (0.33 mol) of ferric sulfate heptahydrate in 324 ml of water containing 37 ml of 28% aqueous ammonia. The mixture was refluxed for 10 minutes. After insoluble matters were filtered off, the filtrate was acidified with conc. hydrochloric acid followed by extracting three times with ethyl acetate. The combined extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to give 4.30 g (24.5%, yield based on 2-methyl-3-nitrotoluene) of the desired 4-methyl-2-indolecarboxylic acid.

^{1}H NMR (DMSO-d_6) δ: 2.49 (3H, s), 6.83 (1H, d, J=6.3Hz), 7.08-7.14 (2H, m), 7.25 (1H, d, J=8.3Hz), 11.7 (1H, br-s), 12.8 (1H, br-s).

The following compounds were prepared in a manner similar to Reference Example 2.

(1) 4-Chloro-2-indolecarboxylic acid:

^{1}H NMR (DMSO-d_6) δ: 7.06 (1H, d, J=2.0Hz), 7.16 (1H, d, J=7.6Hz), 7.22-7.28 (1H, m), 7.42 (1H, d, J=7.9Hz), 12.2 (1H, br-s), 13.2 (1H, br-s).

(2) 6-Chloro-2-indolecarboxylic acid:

^{1}H NMR (DMSO-d_6) δ: 7.04-7.10 (2H, m), 7.43 (1H, d, J=0.7Hz), 7.65 (1H, d, J=8.6Hz), 11.9 (1H, br-s), 13.0 (1H, br-s).

(3) 5-Methyl-2-indolecarboxylic acid:

^{1}H NMR (DMSO-d_6) δ: 2.36 (3H, s), 6.98 (1H, dd, J=1.0, 2.0Hz), 7.04-7.08 (1H, m), 7.30-7.33 (1H, m), 7.40 (1H, s), 11.6 (1H, br-s), 12.9 (1H, br-s).

(4) 6-Methyl-2-indolecarboxylic acid:

^{1}H NMR (DMSO-$_6$) δ: 2.40 (3H, s), 6.87-6.90 (1H, m), 7.00-7.01 (1H, m), 7.21 (1H, s), 7.50 (1H, d, J=8.3Hz), 11.6 (1H, br-s), 12.7 (1H, br-s).

(5) 7-Methyl-2-indolecarboxylic acid:

^{1}H NMR (DMSO-$_6$) δ: 2.52 (3H, s), 6.93-7.02 (2H, m), 7.09 (1H, d, J=2.0Hz), 11.5 (1H, br-s), 12.8 (1H, br-s).

(6) 7-Benzyloxy-2-indolecarboxylic acid:

^{1}H NMR (DMSO-$_6$) δ: 5.27 (2H, s), 6.86 (1H, d, J=7.3Hz), 6.94-7.00 (1H, m), 7.07 (1H, dd, J=2.0, 7.3Hz), 7.17-7.23 (1H, m), 7.31-7.43 (3H, m), 7.65 (2H, d, J=6.9Hz), 11.82 (1H, br-s), 12.81 (1H, br-s).

(7) 4-Benzyloxy-2-indolecarboxylic acid:

^{1}H NMR (DMSO-$_6$) δ: 5.24 (2H, s), 6.62 (1H, d, J=6.9Hz), 7.00-7.17 (3H, m), 7.31-7.44 (3H, m), 7.50-7.53 (2H, m), 11.78 (1H, br-s), 12.85 (1H, br-s).

Reference Example 3

Preparation of Methyl 6-indolecarboxylate

a) Preparation of methyl 4-chloro-3-nitrobenzoate

To a solution of 10.0 g (49.6 mmol) of 4-chloro-3-nitrobenzoic acid in 100 ml of methanol was added dropwise 11.8 g (99.2 mmol) of thionyl chloride at 0°C. The reaction mixture was refluxed for 2 hours and the solvent was then distilled off under reduced pressure. Ice water was added to the resulting residue. The mixture was made basic by the addition of concentrated ammonium hydroxide. The mixture was extracted three times with ethyl acetate. The combined extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure to give 10.9 g (>99%) of the desired methyl 4-chloro-3-nitrobenzoate.

b) Preparation of methyl 3-nitro-4-trimethylsilylethynylbenzoate

A mixture of 10.7 g (49.6 mmol) of methyl 4-chloro-3-nitrobenzoate obtained above, 8.77 g (89.3 mmols) of trimethylsilylacetylene, 0.4 g of dichloro-bis(triphenylphosphine)palladium and 120 ml of triethylamine was heated at 75°C for 3 hours with stirring. The reaction mixture was cooled. After insoluble matters were filtered off, the extract was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain 8.40 g (61.0%) of methyl 3-nitro-4-trimethylsilylethynylbenzoate.

c) Preparation of methyl 4-(2,2-dimethoxyethyl)-3-nitrobenzoate

To a methanol solution of 2.92 g (54.1 mmol) of sodium methoxide was added 3.00 g (10.8 mmol) of methyl 3-nitro-4-trimethylsilylethynylbenzoate prepared above. The mixture was refluxed for 30 minutes. After cooling to 0°C, 5.52 g (54.1 mmol) of acetic acid was added to the reaction mixture and the solvent was then distilled off under reduced pressure. Ice water was poured onto the resulting residue followed by extraction three times with dichloromethane. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure and the residue was purified by silica gel column chromatography to give 2.40 g (82.4%) of methyl 4-(2,2-dimethoxyethyl)-3-nitrobenzoate.

d) Preparation of methyl 3-amino-4-(2,2-dimethoxyethyl)benzoate

To a mixture of 4.40 g (16.3 mmol) of methyl 4-(2,2-dimethoxyethyl)-3-nitrobenzoate in a solvent mixture of 200 ml of methanol and 2 ml of acetic acid was added 0.50 g of 5% palladium-carbon to perform catalytic hydrogenation at ambient temperature under normal pressure and then treat the reaction mixture in a conventional manner. Thus, 4.16 g of methyl 3-amino-4-(2,2-dimethoxyethyl)benzoate was obtained.

e) Preparation of methyl 6-indolecarboxylate

After 4.00 g (16.7 mmol) of methyl 3-amino-4-(2,2-dimethoxyethyl)benzoate obtained above was added to a solution of 5 ml of 1N hydrochloric acid in 15 ml of ethanol, the mixture was heated at 60°C for an hour. The reaction mixture was poured onto ice water followed by extraction three times with ethyl acetate. The combined extracts were then washed with water. After drying over anhydrous magnesium sulfate, the solvent was then distilled off under reduced pressure to give 3.00 g (>99%) of methyl 6-indolecarboxylate.

^{1}H NMR ($CDCl_3$) δ: 3.95 (3H, s), 7.13-7.45 (4H, m), 7.68-7.72 (1H, m), 8.94 (1H, br-s).

Reference Example 4

Preparation of methyl 1-methyl-2-indolecarboxylate

After 2.00 g (12.4 mmol) of 2-indole-carboxylic acid was added to a suspension of 0.99 g (24.8 mmol) of 60% sodium hydride in 40 ml of dimethylformamide, the mixture was stirred at room temperature until the mixture became a transparent solution. A solution of 7.05 g (49.6 mmol) of methyl iodide in 10 ml of dimethylformamide was then added dropwise to the transparent solution at room temperature followed by stirring at the same temperature for 5 hours. The reaction mixture was poured onto ice water. The resulting mixture was then extracted three times with ethyl acetate. The combined extracts were washed with water. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure and the residue was recrystallized from n-hexane to give 1.70 g (72.4%) of methyl 1-methyl-2-indolecarboxylate.

^{1}H NMR ($CDCl_3$) δ: 3.91 (3H, s), 4.08 (3H, s), 7.12-7.18 (1H, m), 7.30 (1H, s), 7.32-7.41 (2H, m), 7.66-7.70 (1H, m).

The following compounds were prepared in a manner similar to Reference Example 4.

(1) Methyl 1-methyl-5-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.82 (3H, s), 3.93 (3H, s), 6.58 (1H, dd, J=1.0, 3.3Hz), 7.11 (1H, d, J=3.3Hz), 7.32 (1H, d, J=8.6Hz), 7.91-7.95 (1H, m), 8.39-8.40 (1H, m).

(2) Methyl 1-methyl-3-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.82 (3H, s), 3.91 (3H, s), 7.24-7.37 (3H, m), 7.77 (1H, s), 8.14-8.20 (1H, m).

(3) Methyl 1-methyl-4-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.84 (3H, s), 3.98 (3H, s), 7.10-7.11 (1H, m), 7.20 (1H, d, J=3.0Hz), 7.24-7.29 (1H, m), 7.53 (1H, d, J=8.2Hz), 7.91 (1H, dd, J=1.0, 7.6Hz).

(4) Methyl 4-chloro-1-methyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.60 (3H, s), 3.75 (3H, s), 6.80-6.83 (1H, m), 6.89-6.95 (2H, m), 7.05 (1H, d, J=0.7Hz).

(5) Methyl 5-chloro-1-methyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.64 (3H, s), 3.78 (3H, s), 6.93 (1H, s), 6.97-7.02 (2H, m), 7.36 (1H, t, J=1.3Hz).

(6) Methyl 6-chloro-1-methyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.91 (3H, s), 4.04 (3H, s), 7.09-7.13 (1H, m), 7.25-7.26 (1H, m), 7.38-7.39 (1H, m), 7.56-7.59 (1H, m).

(7) Methyl 7-chloro-1-methyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.91 (3H, s), 4.47 (3H, s), 6.99 (1H, m), 7.26-7.30 (2H, m), 7.52-7.56 (1H, m).

(8) Methyl 1,4-dimethyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 2.56 (3H, s), 3.92 (3H, s), 4.07 (3H, s), 6.93-6.96 (1H, m), 7.17-7.29 (2H, m), 7.33 (1H, d, J=0.7Hz).

(9) Methyl 1,5-dimethyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 2.44 (3H, s), 3.90 (3H, s), 4.05 (3H, s), 7.16-7.29 (3H, m), 7.42-7.45 (1H, m).

(10) Methyl 1,6-dimethyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 2.51 (3H, s), 3.90 (3H, s), 4.05 (3H, s), 6.99 (1H, dd, J=1.0, 8.3Hz), 7.12-7.16 (1H, m), 7.24-7.26 (1H, m), 7.55 (1H, d, J=8.2Hz), 7.42-7.45 (1H, m).

(11) Methyl 1,7-dimethyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 2.80 (3H, s), 3.89 (3H, s), 4.35 (3H, s), 6.97 (2H, m), 7.25-7.27 (1H, m), 7.26 (1H, s), 7.48 (1H, d, J=7.3Hz).

(12) Methyl 1-methyl-5-methoxy-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.85 (3H, s), 3.90 (3H, s), 4.05 (3H, s), 7.00-7.09 (2H, m), 7.19-7.30 (2H, m).

(13) Benzyl 1-benzyl-5-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 5.33 (2H, s), 5.38 (2H, s), 6.64 (1H, d, J=3.3Hz), 7.06-7.49 (12H, m), 7.92 (1H, dd, J=1.7, 8.9Hz), 8.45-8.46 (1H, m).

(14) Isopropyl 1-isopropyl-5-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.38 (6H, d, J=6.3Hz), 1.53 (6H, d, J=6.6Hz), 4.62-4.75 (1H, m), 5.21-5.35 (1H, m), 6.60 (1H, d, J=3.3Hz), 7.27 (1H, d, J=3.3Hz), 7.36 (1H, d, J=8.6Hz), 7.90 (1H, dd, J=1.7, 8.6Hz), 8.38 (1H, d, J=1.7Hz).

Reference Example 5

Preparation of methyl 1-methyl-6-indolecarboxylate

The reaction was carried out in a manner similar to Reference Example 4 except for using 3.00 (17.1 mmol) of methyl 6-indolecarboxylate, 0.68 g (17.1 mmol) of 60% sodium hydroxide, 4.86 g (34.4 mmol) of methyl iodide and 60 ml of dimethylformamide. Thus 2.75 g (86.9%) of methyl 1-methyl-6-indolecarboxylate was obtained.

^{1}H NMR ($CDCl_3$) δ: 3.86 (3H, s), 3.95 (3H, s), 6.51-6.53 (1H, m), 7.21 (1H, d, J=3.3Hz), 7.63 (1H, d, J=8.6Hz), 7.78-7.82 (1H, m), 8.10 (1H, s).

The following compounds were prepared in a manner similar to Reference Example 5.

(1) Ethyl 4-methoxy-1-methyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7.3Hz), 3.96 (3H, s), 4.06 (3H, s), 4.35 (2H, dd, J=7.3, 14.2Hz), 6.50 (1H, d, J=7.6Hz), 6.98 (1H, d, J=8.6Hz), 7.24-7.30 (1H, m), 7.42 (1H, d, J=0.7Hz).

(2) Ethyl 6-methoxy-1-methyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.37-1.42 (3H, m), 3.89 (3H, s), 4.03 (3H, s), 4.31-4.39 (2H, m), 6.75 (1H, s), 6.80-6.84 (1H, m), 7.25 (1H, s), 7.53 (1H, d, J=8.9Hz).

(3) Ethyl 1-methyl-4-nitro-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7.3Hz), 4.17 (3H, s), 4.39-4.47 (2H, m), 7.41-7.48 (1H, m), 7.74-7.77 (1H, m), 7.96 (1H, d, J=1.0Hz), 8.18-8.21 (1H, m).

(4) Ethyl 1-methyl-6-nitro-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.41-1.46 (3H, m), 4.17 (3H, s), 4.38-4.46 (2H, m), 7.34 (1H, d, J=1.0Hz), 7.75 (1H, dd, J=0.7, 8.9Hz), 8.03 (1H, dd, J=2.0, 8.9Hz), 8.39 (1H, d, J=2.0Hz).

(5) Ethyl 1-methyl-5-nitro-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.41-1.46 (3H, m), 4.14 (3H, s), 4.41 (2H, dd, J=7.3, 14.2Hz), 7.42-7.46 (2H, m), 8.22-8.26 (1H, m), 8.66 (1H, d, J=2.0Hz).

(6) Ethyl 1-methyl-7-nitro-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7.3Hz), 4.00 (3H, s), 4.37-4.45 (2H, m), 7.20 (1H, t, J=7.9Hz), 7.43 (1H, s), 7.85-7.93 (2H, m).

(7) Methyl 1-benzyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.86 (3H, s), 5.84 (2H, s), 7.02-7.06 (2H, m), 7.13-7.44 (7H, m), 7.70-7.73 (1H, m).

(8) Methyl 1-benzyl-3-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.91 (3H, s), 5.34 (2H, s), 7.13-7.17 (2H, m), 7.20-7.36 (6H, m), 7.85 (1H, s), 8.17-8.21 (1H, m).

(9) Methyl 1-isopropyl-3-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.56 (6H, d, J=6.9Hz), 3.92 (3H, s), 4.64-4.74 (1H, m), 7.24-7.31 (2H, m), 7.39-7.42 (2H, m), 7.96 (1H, s), 8.15-8.20 (1H, m).

(10) Ethyl 1,3-dimethyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.42-1.47 (3H, m), 2.59 (3H, s), 4.01 (3H, s), 4.37-4.45 (2H, m), 7.10-7.18 (1H, m), 7.31-7.38 (2H, m), 7.64-7.67 (1H, m).

(11) Ethyl 1-methyl-4-methylsulfonyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) 6: 1.41-1.46 (3H, m), 3.14 (3H, s), 4.16 (3H, s), 4.41 (2H, dd, J=7.3, 14.2Hz), 7.48 (1H, dd, J=7.3, 8.3Hz), 7.68-7.71 (2H, m), 7.81-7.84 (1H, m).

(12) Ethyl 1-methyl-6-methylsulfonyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.41-1.46 (3H, m), 3.11 (3H, s), 4.16 (3H, s), 4.37-4.45 (2H, m), 7.34 (1H, d, J=0.7Hz), 7.62-7.70 (2H, m), 7.83 (1H, dd, J=0.7, 8.6 Hz), 8.07 (1H, d, J=0.7Hz).

(13) Methyl 4-fluoro-1-methyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.92 (3H, s), 4 09 (3H, s), 6.77-6.83 (1H, m), 7.16 (1H, d, J=8.3Hz), 7.23-7.31 (1H, m), 7.36 (1H, s).

(14) Methyl 4-bromo-1-methyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.93 (3H, s), 4.08 (3H, s), 7.16-7.26 (1H, m), 7.31-7.35 (3H, m).

(15) Methyl 1-(2-naphthylmethyl)-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.86 (3H, s), 6.00 (2H, s), 7.14-7.32 (3H, m), 7.37-7.43 (5H, m), 7.66-7.78 (4H,

m).

(16) Methyl 1-(2-phenylethyl)-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.06 (2H, t, J=7.9Hz), 3.90 (3H, s), 4.74-4.80 (2H, m), 7.11-7.33 (9H, m), 7.66-7.69 (1H, m).

(17) Methyl 1-(4-bromobenzyl)-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.87 (3H, s), 5.79 (2H, s), 6.92 (2H, dd, J=2.0, 6.6Hz), 7.15-7.23 (1H, m), 7.31-7.38 (5H, m), 7.70-7.74 (1H, m).

(18) Methyl 1-(4-nitrobenzyl)-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.87 (3H, s), 5.93 (2H, s), 7.14-7.41 (5H, m), 7.42 (1H, d, J=0.7Hz), 7.73-7.77 (1H, m), 8.09-8.14 (2H, m).

(19) Methyl 1-(3-phenylpropyl)-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 2.06-2.22 (2H, m), 2.69 (2H, d, J=8.0Hz), 3.90 (3H, s), 4.60 (2H, t, J=8.0Hz), 7.05-7.40 (9H, m), 7.66 (1H, d, J=8.0Hz).

(20) Methyl 1-(2-methoxyethyl)-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.28 (3H, s), 3.73 (2H, t, J=5.9Hz), 3.91 (3H, s), 4.74 (2H, t, J=5.9Hz), 7.14 (1H, ddd, J=1.0, 6.9, 7.4Hz), 7.31 (1H, d, J=0.7Hz), 7.36 (1H, dd, J=1.3, 6.9Hz), 7.48 (1H, dd, J=0.7, 8.6Hz), 7.66 (1H, dd, J=1.1, 8.3Hz).

(21) Methyl 1-(2-diethylaminoethyl)-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.03 (6H, t, J=7.3Hz), 2.61 (4H, q, J=7.3Hz), 2.70-2.82 (2H, m), 3.91 (3H, s), 4.58-4.70 (2H, m), 7.14 (1H, ddd, J=1.3, 6.7, 8.6Hz), 7.27 (1H, d, J=1.0Hz), 7.34 (1H, ddd, J=1.0, 6.7, 7.1Hz), 7.43 (1H, dd, J=1.0, 8.6Hz), 7.61-7.71 (1H, m).

(22) Ethyl 4-chloro-1-(2-diethylaminoethyl)-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.00 (6H, t, J=7.3Hz), 1.42 (3H, t, J=7.3Hz),2.59 (4H, q, J=7.3Hz), 2.69-2.80 (2H, m), 4.38 (2H, q, J=7.3Hz), 4.56-4.68 (2H, m), 7.14 (1H, dd, J=1.0, 7.3Hz), 7.18-7.28 (1H, m), 7.29-7.35 (1H, m), 7.37 (1H, d, J=0.7Hz).

(23) Preparation of methyl 1-[2-(2-tetrahydropyranyl)oxyethyl]-2-indolecarboxylate:

The reaction was carried out in a manner similar to Reference Example 5 except for using 2.0 g (11.4 mmol) of methyl 2-indolecarboxylate, 0.55 g (13.7 mmol) of 60% sodium hydroxide, 3.63 g (13.7 mmol) of 2-(2-iodoethoxy)tetrahydropyran (prepared from 2-iodoethanol and 3,4-dihydro-2H-pyran) and 50 ml of dimethylformamide. Thus, 2.87 g (83.0%) of methyl 1-[2-(2-tetrahydropyranyl)oxyethyl]-2-indolecarboxylate was obtained.

^{1}H NMR ($CDCl_3$) δ: 1.27-1.75 (6H, m), 3.26-3.54 (2H, m), 3.75 (1H, dt, J=4.6, 10.2Hz), 4.03 (1H, dt, J=4.6, 10.2Hz), 4.47 (1H, t, J=3.0Hz), 4.80 (2H, t, J=3.7Hz), 7.13 (1H, t, J=7.0Hz), 7.22-7.38 (2H, m), 7.53 (1H, d, J=8.0Hz), 7.65 (1H, d, J=8.0Hz).

(24) Methyl 1-[3-(2-tetrahydropyranyl)oxypropyl]-2-indolecarboxylate:

The title compound was prepared in a manner similar to Reference Example 5 (23) except that 2-(3-iodopropoxy)tetrahydropyran was used in place of 2-(2-iodoethoxy)tetrahydrophyran.

^{1}H NMR ($CDCl_3$) δ: 1.42-1.97 (6H, m), 2.11 (2H, dt, J=5.9, 11.2Hz), 3.33 (1H, dt, J=7.9, 8.3Hz), 3.40-3.55 (1H, m), 3.72-3.88 (2H, m), 3.94 (3H, s), 4.52 (1H, dd, J=3.0, 4.3Hz), 4.69 (2H, dt, J=0.9, 1.7Hz), 7.14 (1H, ddd, J=1.0, 7.0, 7.9Hz), 7.27-7.37 (2H, m), 7.48 (1H, dd, J=0.9, 8.5Hz), 7.66 (1H, dt, J=1.0, 7.9Hz).

(25) Synthesis of methyl 1-(3-tert-butoxycarbonylaminopropyl)-2-indolecarboxylate:

The reaction was carried out in a manner similar to Reference Example 5 except for using 5.00 g (28.5 mmol) of methyl 2-indolecarboxylate, 1.26 g (31.4 mmol) of 60% sodium hydroxide, 12.3 g (43.2 mmol) of tert-butyl N-(3-iodopropyl)carbamate (prepared from 3-iodopropylamine and di-tert-butyl dicarbonate) and 60 ml of dimethylformamide. Thus, 2.54 g (27%) of methyl 1-(3-tert-butoxycarbonylaminopropyl)-2-indolecarboxylate was obtained.

^{1}H NMR ($CDCl_3$) δ: 1.45 (9H, s), 1.90-2.10 (2H, m), 3.00-3.20 (2H, m), 3.91 (3H, s), 4.62 (2H, t, J=6.9Hz), 4.98 (1H, br-s), 7.06-7.20 (1H, m), 7.28-7.44 (3H, m), 7.68 (1H, d, J=7.3Hz).

(26) Methyl 1-(2-tert-butoxycarbonylaminoethyl)-2-indolecarboxylate:

The title compound in a manner similar to Reference Example 5 (25) except that tert-butyl N-(2-iodopropyl)carbamate was used in place of tert-butyl N-(3-iodopropyl)carbamate.

^{1}H NMR ($CDCl_3$) δ: 1.41 (9H, s), 3.53 (2H, t, J=5.9Hz), 3.90 (3H, s), 4.68 (2H, t, J=6.3Hz), 4.60-4.80 (1H, m), 7.15 (1H, ddd, 1H, J=1.0, 6.9, 7.4Hz), 7.27-7.38 (2H, m), 7.48 (1H, d, J=8.3Hz), 7.66 (1H, d, J=7.9Hz).

(27) Ethyl 1-methyl-4-(2-tetrahydropyranyl)oxymethyl-2-indolecarboxylate:

The title compound was prepared in a manner similar to Reference Example 5.

^{1}H NMR ($CDCl_3$) δ: 1.39-1.44 (3H, m), 1.53-1.91 (6H, m), 3.50-3.61 (1H, m), 3.84-4.03 (1H, m), 4.09 (3H, s), 4.34-4.42 (2H, m), 4.75 (1H, t, J=3.6Hz), 4.83 (1H, d, J=12.2Hz), 5.08 (1H, d, J=12.2Hz), 7.18 (1H,

t, J=4.0Hz), 7.32-7.33 (2H, m), 7.42 (1H, s).

(28) Ethyl 4-chloro-1-[4-(2-tetrahydropyranyl)oxybutyl]-2-indolecarboxylate:

The title compound was prepared in a manner similar to Reference Example 5 (23) except taht 2-(4-iodobutoxy)tetrahydropyran and ethyl 4-chloro-2-indolecarboxylate was used in place of 2-(2-iodoethoxy)tetrahydropyran and methyl 2-indolecarboxylate.

^{1}H NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7.3Hz), 1.41-2.00 (10H, m), 3.32-3.56 (2H, m), 3.68-3.90 (2H, m), 4.38 (2H, q, J=7.3Hz), 4.55 (1H, t, J=4.0Hz), 4.60 (2H, t, J=7.6Hz), 7.13 (1H, dd, J=1.0, 7.6Hz), 7.22 (1H, d, J=8.2Hz), 7.32 (1H, d, J=8.3Hz), 7.39 (1H, s).

(29) Methyl 1-(3:4-isopropylidenedioxybutyl)-2-indolecarboxylate:

The title compound was prepared in a manner similar to Reference Example 5 except that 3,4-isopropylidenedioxybutyl iodide was used in place of methyl iodide.

^{1}H NMR ($CDCl_3$) δ: 1.34 (3H, s), 1.46 (3H, s), 1.90-2.18 (2H, m), 3.52 (1H, dd, J=6.9, 7.9Hz), 3.91 (3H, s), 3.97 (1H, dd, J=5.9, 7.9Hz), 4.01-4.17 (1H, m), 4.58-4.80 (2H, m), 7.15 (1H, ddd, J=1.0, 6.9, 7.4Hz), 7.31 (1H, d, J=0.7Hz), 7.35 (1H, ddd, J=1.3, 6.9, 7.6Hz), 7.47-7.55 (1H, m), 7.63-7.70 (1H, m).

(30) Methyl-1-[2-[1-(4-methyl-2,6,7-trioxabicyclo-[2.2.2]octyl)]ethyl]-2-indolecarboxylate:

The title compound was prepared in a manner similar to Reference Example 5 except that 2-[1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl]ethyl iodide was used in place of methyl iodide.

^{1}H NMR ($CDCl_3$) δ: 0.79 (3H, s), 2.17 (2H, ddd, J=2.6, 5.3, 7.9Hz), 3.89 (6H, s), 3.90 (3H, s), 5,87 (2H, ddd, J=2.3, 5.6, 7.9Hz), 7.12 (1H, ddd, J=1.0, 6.9, 7.4Hz), 7.27 (1H, d, J=0.7Hz), 7.32 (1H, ddd, J=1.3, 6.9, 7.6Hz), 7.48 (1H, dd, J=0.7, 8.6Hz), 7.65 (1H, ddd, J=1.0, 1.5, 8.3Hz).

The following compounds were prepared in a manner similar to Reference Example 5.

(31) Methyl 4-benzyloxy-1-methyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.89 (3H, s), 4.06 (3H, s), 5.22 (2H, s), 6.57 (1H, d, J=7.6Hz), 6.99 (1H, d, J=8.6Hz), 7.22-7.28 (1H, m), 7.30-7.51 (6H, m).

(32) Methyl 6-benzyloxy-1-methyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.89 (3H, s), 4.02 (3H, s), 5.15 (2H, s), 6.85 (1H, d, J=2.31Hz), 6.91 (1H, dd, J=2.3, 8.6Hz), 7.24 (1H, d, J=1.0Hz), 7.34-7.44 (3H, m), 7.47-7.52 (2H, m), 7.53-7.57 (1H, m).

(33) Methyl 7-benzyloxy-1-methyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.89 (3H, s), 4.38 (3H, s), 5.19 (2H, s), 6.78 (1H, d, J=8.6Hz), 6.97-7.03 (1H, m), 7.24-7.27 (2H, m), 7.33-7.51 (5H, m).

Reference Example 6

Preparation of methyl 2-indolecarboxylate

To 300 ml of a methanol solution of 30.0 g (186.2 mmol) of 2-indolecarboxylic acid was dropwise added 44.3 g (372.3 mmol) of thionyl chloride at 0°C. The reaction mixture was refluxed for 2 hours and the solvent was then distilled off under reduced pressure. Ice water was poured onto the resulting residue. The mixture was made basic by the addition of concentrated ammonium hydroxide. The mixture was extracted three times with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure to give 32.34 g (99.2%) of methyl 2-indolecarboxylate.

^{1}H NMR ($CDCl_3$) δ: 3.95 (3H, s), 7.13-7.45 (4H, m), 7.69 (1H, dd, J=1.0, 7.9Hz), 8.91 (1H, br-s).

The following compounds were prepared in a manner similar to Reference Example 6.

(1) Methyl 3-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.93 (3H, s), 7.24-7.31 (2H, m), 7.38-7.45 (1H, m), 7.93 (1H, d, J=3.0Hz), 8.17-8.22 (1H, m), 8.63 (1H, br-s).

(2) Methyl 4-fluoro-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.96 (3H, s), 6.78-6.85 (1H, m), 7.18-7.30 (3H, m), 8.99 (1H, br-s).

(3) Methyl 4-bromo-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.97 (3H, s), 7.17 (1H, dd, J=7.6, 8.3Hz), 7.28 (1H, dd, J=1.0, 2.3Hz), 7.32-7.39 (2H, m), 9.05 (1H, br-s).

(4) Methyl 7-benzyloxy-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.93 (3H, s), 5.21 (2H, s), 6.80 (1H, d, J=6.9Hz), 7.01-7.08 (1H, m), 7.19 (1H, dd, J=2.3, 4.3Hz), 7.24-7.31 (1H, m), 7.35-7.51 (5H, m), 9.07 (1H, br-s).

(5) Methyl 4-benzyloxy-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 3.93 (3H, s), 5.22 (2H, s), 6.58 (1H, d, J=7.6Hz), 7.03 (1H, d, J=8.3Hz), 7.19-7.26 (1H, m), 7.31-7.44 (4H, m), 7.50 (2H, d, J=7.3Hz), 8.84 (1H, br-s).

Reference Example 7

Preparation of methyl 5-indolecarboxylate

A mixture of 1.00 g (6.21 mmol) of 5-indolecarboxylic acid and 50 ml of 10% hydrogen chloride/ methanol was refluxed for 2 hours. The reaction mixture was then poured onto ice water followed by neutralization with sodium bicarbonate. The mixture was extracted three times with ethyl acetate. The combined extracts were washed with aqueous sodium bicarbonate solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure to give 0.42 g (38.6%) of methyl 5-indole-carboxylate.

^1H NMR ($CDCl_3$) δ: 3.93 (3H, s), 6.64-6.66 (1H, m), 7.26-7.29 (1H, m), 7.40 (1H, dd, J=0.7, 8.6Hz), 7.91 (1H, dd, J=1.7, 8.6Hz), 8.3-8.6 (2H, m).

Reference Example 8

Preparation of methyl 1-isopropyl-5-indolecarboxylate

A mixture of 2.20 g (8.97 mmol) of isopropyl 1-isopropyl-5-indolecarboxylate, 100 ml of 2N sodium hydroxide solution and 100 ml of ethanol was refluxed for an hour. The solvent was then distilled off under reduced pressure. Thereafter water was added to the residue and the resulting mixture was acidified with conc. hydrochloric acid. The precipitated solid was filtered and dried under reduced pressure to give 2.00 g of crude 1-isopropyl-5-indole-carboxylic acid. The reaction was carried out in a manner similar to Reference Example 4 using 2.00 g of the crude 1-isopropyl-5-indolecarboxylic acid, 0.44 g (11.1 mmol) of 60% sodium hydride, 2.87 g (20.2 mmol) of methyl iodide and 50 ml of dimethylformamide. Thus, 1.64 g (84.2%; yield based on isopropyl 1-isopropyl-5-indolecarboxylic acid) was obtained.

^1H NMR ($CDCl_3$) δ: 1.54 (6H, d, J=6.9Hz), 3.93 (3H, s), 4.65-4.75 (1H, m), 6.61 (1H, d, J=3.3Hz), 7.28 (1H, d, J=3.3Hz), 7.37 (1H, d, J=8.6Hz), 7.9 (1H, dd, J=1.7, 8.6Hz), 8.39 (1H, d, J=1.7Hz).

Reference Example 9

Preparation of 7-chloro-2-indolecarboxylic acid

A mixture of 3.40 g (15.2 mmol) of ethyl 7-chloro-2-indolecarboxylate, 100 ml of 2N sodium hydroxide solution and 100 ml of ethanol was refluxed for an hour. The solvent was then distilled off under reduced pressure. Thereafter ice water was added to the residue and the resulting mixture was acidified with conc. hydrochloric acid and extracted three times with ethyl acetate. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure to give 2.85 g (95.8%) of 7-chloro-2-indolecarboxylic acid.

^1H NMR (DMSO-d_6) δ: 7.04-7.09 (1H, m), 7.19 (1H, d, J=2.0Hz), 7.30 (1H, dd, J=1.0, 7.6Hz), 7.62 (1H, d, J=8.3Hz), 11.9 (1H, br-s), 13.1 (1H, br-s).

Reference Example 10

Preparation of 1-isopropyl-2-indolecarboxylic acid

The reaction was carried out in a manner similar to Reference Example 4, using 6.00 g (34.2 mmol) of methyl 2-indolecarboxylate, 1.36 g (34.2 mmol) of 60% sodium hydroxide, 6.40 g (37.7 mmol) of isopropyl iodide and 100 ml of dimethylformamide. The mixture of methyl 1-isopropyl-2-indolecarboxylate and isopropyl 1-isopropyl-2-indolecarboxylate was obtained. The reaction was carried out in a manner similar to Reference Example 9, using the thus obtained mixture, 150 ml of 2N sodium hydroxide solution and 150 ml of ethanol. Thus 3.71 g (53.3%) of 1-isopropyl-2-indolecarboxylic acid was obtained.

^1H NMR (DMSO-d_6) δ: 1.58 (6H, d, J=6.9Hz), 5.74-5.85 (1H, m), 7.05-7.11 (1H, m), 7.19-7.28 (2H, m), 7.64-7.72 (2H, m), 12.9 (1H, br-s).

Reference Example 11

Preparation of methyl 1-methyl-7-indolecarboxylate

a) Preparation of ethyl 7-carbomethoxy-1-methyl-2-indolecarboxylate

After 5.00 g (20.2 mmol) of ethyl 7-carbomethoxy-2-indolecarboxylate obtained in a manner similar to Reference Example 1 was added to a suspension of 0.81 g (20.2 mmol) of 60% sodium hydride in 80 ml of dimethylformamide, the mixture was stirred at room temperature until the mixture became a transparent solution. A solution of 5.74 g (40.4 mmol) of methyl iodide was then added dropwise to the transparent solution at room temperature followed by stirring at 50°C for an hour. The reaction solution was poured onto ice water. The resulting mixture was then extracted three times with ethyl acetate and the combined extracts were washed with water. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure and the residue was isolated and purified by silica gel column chromatography to give 5.20 g (98.5%) of ethyl 7-carbomethoxy-1-methyl-2-indolecarboxylate.

b) Preparation of 1-methylindole-2,7-dicarboxylic acid

A mixture of 5.20 g (19.9 mmol) of ethyl 7-carbomethoxy-1-methyl-2-indolecarboxylate, 90 ml of 2N sodium hydroxide and 150 ml of ethanol was refluxed for 3 hours. The reaction mixture was concentrated under reduced pressure and ice water was added to the residue. 2N hydrochloric acid was added to acidify the reaction mixture. The precipitated solid was filtered and dried under reduced pressure to give 4.70 g (>99%) of 1-methylindole-2,7-dicarboxylic acid.

c) Preparation of 1-methyl-7-indolecarboxylic acid

A mixture of 4.60 g (21.0 mmol) of 1-methylindole-2,7-dicarboxylic acid, 0.5 g of copper (II) oxide and 50 ml of quinoline was stirred for an hour with heating at 180°C. After cooling, the reaction mixture was poured onto 200 ml of 2N hydrochloric acid. The mixture was extracted three times with ethyl acetate and the combined extracts were washed with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was isolated and purified by silica gel column chromatography to give 1.82 g (49.0%) of 1-methyl-7-indolecarboxylic acid.

d) Preparation of methyl 1-methyl-7-indolecarboxylate

To 70 ml of a methanol solution of 1.82 g (10.4 mmol) of 1-methyl-7-indolecarboxylic acid was added dropwise 3.09 g (26.0 mmol) of thionyl chloride at 0°C. The reaction mixture was refluxed for 2 hours and the solvent was then distilled off under reduced pressure. Ice water was poured onto the resulting residue and ammonium hydroxide was added to render the mixture alkaline. The mixture was extracted three times with ethyl acetate. The combined extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure. The residue was isolated and purified by silica gel column chromatography to give 1.16 g (59.0%) of methyl 1-methyl-7-indolecarboxylate.

^1H NMR ($CDCl_3$) δ: 3.88 (3H, s), 3.96 (3H, s), 6.54 (1H, d, J=3.3Hz), 7.10 (1H, t, J=7.6Hz), 7.67 (1H, d, J=7.3Hz), 7.75-7.78 (1H, m).

Reference Example 12

Preparation of ethyl 7-benzyloxy-4-chloro-2-indolecarboxylate

a) Preparation of 3-benzyloxy-6-chloro-2-nitrotoluene

A mixture of 1.50 g (8.00 mmols) of 4-chloro-3-methyl-2-nitrophenol, 1.50 g (8.80 mmols) of benzyl bromide, 2.43 g (17.6 mmols) of potassium carbonate and 70 ml of acetone was refluxed for 2 hours. Thereafter insoluble matters were filtered off and the filtrate was concentrated under reduced pressure. The residue was isolated and purified by silica gel column chromatography to give 2.22 g (>99%) of 3-benzyloxy-6-chloro-2-nitrotoluene.

b) Preparation of ethyl (3-benzyloxy-6-chloro-2-nitrophenyl)pyruvate

Diethyl oxalate, 1.20 g (7.92 mmol), was added dropwise to a suspension of 0.67 g (7.92 mmol) of potassium ethoxide in diethyl ether (50 ml) at room temperature. Subsequently 2.00 g (7.20 mmol) of 3-benzyloxy-6-chloro-2-nitrotoluene was added to the mixture followed by stirring for 4 hours at room temperature. The re-

action solution was poured onto 1N hydrochloric acid and the mixture was extracted twice with diethyl ether. The combined extracts were washed with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was isolated and purified by silica gel column chromatography to give 1.60 g (53.5%) of ethyl (3-benzyloxy-6-chloro-2-nitrophenyl)pyruvate.

c) Preparation of ethyl 7-benzyloxy-4-chloro-2-indolecarboxylate

A mixture of 1.60 g (4.24 mmol) of ethyl (3-benzyloxy-4-chloro-2-nitrophenyl)pyruvate, 22.9 g (29.7 mmol) of 20% titanium trichloride solution and 60 ml of acetone was stirred at room temperature for 3 hours. The reaction mixture was poured onto ice water and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with saturated sodium hydrogencarbonate solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to give 0.50 g (35.8%) of ethyl 7-benzyloxy-4-chloro-2-indole-carboxylate.

^{1}H NMR ($CDCl_3$) δ: 1.39-1.44 (3H, m), 4.40 (2H, dd, J=6.9, 14.2Hz), 5.18 (2H, s), 6.69 (1H, d, J=8.3Hz), 7.01 (1H, d, J=8.3Hz), 7.26-7.27 (1H, m), 7.35-7.48 (5H, m), 9.15 (1H, br-s).

Reference Example 13

Preparation of ethyl 6-benzyloxy-4-chloro-2-indolecarboxylate

a) Preparation of ethyl 3-(4-benzyloxy-2-chlorophenyl)-2-azidopropenoate

An ethanol solution, 70 ml, containing 5.40 g (21.9 mmol) of 4-benzyloxy-2-chlorobenzaldehyde and 11.3 g (87.6 mmol) of ethylazide acetate was gradually added dropwise to 70 ml of an ethanol solution of 5.95 g (87.6 mmol) of sodium ethoxide at -10°C. After stirring at -10°C for further 5 hours, the reaction temperature was slowly elevated to room temperature. The reaction mixture was poured onto 200 ml of saturated ammonium chloride aqueous solution and the mixture was extracted three times with ethyl acetate. The combined extracts were then washed with saturated ammonium chloride solution and next with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 4.50 g (57.5%) of ethyl 3-(4-benzyloxy-2-chlorophenyl)-2-azidopropenoate.

b) Preparation of ethyl 6-benzyloxy-4-chloro-2-indolecarboxylate

A solution of 4.50 g (12.6 mmols) of ethyl 3-(4-benzyloxy-2-chlorophenyl)-2-azidopropenoate in 100 ml of toluene was refluxed for 3 hours. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 3.73 g (89.8%) of ethyl 6-benzyloxy-4-chloro-2-indolecarboxylate.

^{1}H NMR ($CDCl_3$) δ: 1.38-1.43 (3H, m), 4.35-4.43 (2H, m), 5.09 (2H, s), 6.79 (1H, dd, J=0.7, 2.0Hz), 6.95 (1H, d, J=2.0Hz), 7.23-7.24 (1H, m), 7.31-7.45 (5H, m), 8.94 (1H, br-s).

Reference Example 14

Preparation of methyl 1-(2-carbamoylethyl)-2-indolecarboxylate

a) Preparation of methyl 1-(2-cyanoethyl)-2-indolecarboxylate

After 3.63 g (68.4 mmol) of acrylonitrile and 2.2 ml of 40% methanol solution of N-benzyltrimethylammonium hydroxide was added to a solution of 10.0 g (57.1 mmol) of methyl 2-indolecarboxylate in 150 ml of 1,4-dioxane, the mixture was stirred at 55°C for an hour. The reaction mixture was concentrated under reduced pressure. The resulting residue was added to a mixture of 5 ml of acetic acid and 500 ml of water. The aqueous layer was extracted twice with methylene chloride and the combined extracts were washed with water. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to give 13.0 g of methyl 1-(2-cyano-ethyl)-2-indolecarboxylate.

b) Preparation of methyl 1-(2-carbamoylethyl)-2-indolecarboxylate

A mixture of 3.12 g (13.7 mmol) of methyl 1-(2-cyanoethyl)-2-indolecarboxylate, 30 ml of 10% sodium carbonate solution, 30 ml of 30% hydrogen peroxide and 100 ml of acetone was stirred at room temperature for 4 hours. Next, the reaction mixture was cooled to 0°C and 10% sodium sulfite solution was added dropwise to decompose an excess of the peroxide. The most of acetone in the reaction mixture was then distilled off and the concentrate was extracted three times with ethyl acetate. The combined extracts were washed with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 2.30 g (68%) of methyl 1-(2-carbamoylethyl)-2-indolecarboxylate.

^{1}H NMR (CDCl$_3$) δ: 2.75 (2H, ddd, J=1.7, 5.9, 7.6Hz), 3.92 (3H, s), 4.85 (2H, ddd, J=1.7, 5.9, 7.6Hz), 5.37 (1H, br-s), 5.72 (1H, br-s), 7.16 (1H, ddd, J=1.0, 6.9, 7.4Hz), 7.32 (1H, d, J=1.0Hz), 7.37 (1H, ddd, J=1.0, 7.3, 7.8Hz), 7.53 (1H, dd, J=0.8, 8.4Hz), 7.67 (1H, dt, J=1.0, 7.9Hz).

The following compound was prepared in a manner similar to Reference Example 14.

(1) Ethyl 1-(2-carbamoylethyl)-4-chloro-2-indolecarboxylate:

^{1}H NMR (CDCl$_3$) δ: 1.43 (3H, t, J=7.3Hz), 2.65-2.82 (1H, m), 4.39 (2H, q, J=7.3Hz), 4.84 (2H, ddd, J=1.0, 6.3, 7.3Hz), 5.45 (1H, br-s), 5.68 (1H, br-s), 7.14 (1H, d, J=7.9Hz), 7.26 (1H, dd, J=7.6, 8.2Hz), 7.41 (1H, d, J=1.0Hz), 7.45 (1H, d, J=8.6Hz).

Reference Example 15

Preparation of methyl 7-carbamoylmethoxy-1-methyl-2-indolecarboxylate

a) Preparation of methyl 7-hydroxy-1-methyl-2-indolecarboxylate

In a solvent mixture of 50 ml of tetrahydrofuran and 50 ml of methanol was dissolved 2.31 g (7.82 mmol) of methyl 7-benzyloxy-1-methyl-2-indolecarboxylate. After 0.5 g of 10% palladium/carbon was added to the solution, catalytic hydrogenation was performed at ambient temperature under normal pressure. After completion of the reaction, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 1.63 g (>99%) of methyl 7-hydroxy-1-methyl-2-indolecarboxylate.

b) Preparation of methyl 7-carbamoylmethoxy-1-methyl-2-indolecarboxylate

After 0.50 g (2.44 mmol) of methyl 7-hydroxy-1-methyl-2-indolecarboxylate was added to a suspension of 0.01 g (2.44 mmol) of 60% sodium hydride in 25 ml of dimethyl-formamide, the mixture was stirred at room temperature until the mixture became a transparent solution. Then 0.25 g (2.68 mmols) of 2-chloroacetamide was added dropwise to the transparent solution at room temperature followed by stirring at 50°C for an hour. The reaction mixture was poured onto ice water. The resulting mixture was then extracted three times with ethyl acetate. The combined extracts were washed with water. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to give 0.54 g (84.4%) of methyl 7-carbamoylmethoxy-1-methyl-2-indolecarboxylate.

^{1}H NMR (CDCl$_3$) δ: 3.91 (3H, s), 4.41 (3H, s), 4.67 (2H, s), 5.70 (1H, br-s), 6.41 (1H, br-s), 6.70-6.73 (1HI m), 7.03 (1H, t, J=7.9Hz), 7.26 (1H, s), 7.31-7.34 (1H, m).

The following compounds were synthesized in a manner similar to Reference Example 15.

(1) Methyl 1-methyl-7-(2-phenylethoxy)-2-indolecarboxylate:

^{1}H NMR (CDCl$_3$) δ: 3.17-3.22 (2H, m), 3.87 (3H, s), 4.24 (3H, s), 4.31-4.36 (2H, m), 6.68 (1H, d, J=7.6Hz), 6.94-7.00 (1H, m), 7.18-7.35 (7H, m).

(2) Methyl 1-methyl-7-(3-phenylpropoxy)-2-indolecarboxylate:

^{1}H NMR (CDCl$_3$) δ: 2.16-2.26 (2H, m), 2.84-2.90 (2H, m), 3.89 (3H, s), 4.07-4.12 (2H, m), 4.43 (3H, s), 6.64 (1H, d, J=6.9Hz), 6.97 (1H, t, J=7.9Hz), 7.18-7.23 (5H, m), 7.25-7,33 (2H, m).

(3) Ethyl 7-carbamoylmethoxy-4-chloro-1-methyl-2-indolecarboxylate:

^{1}H NMR (CDCl$_3$) δ: 1.33-1.36 (3H, m), 4.29-4,37 (5H, m), 4.60 (2H, s), 6.69 (1H, d, J=8.3Hz), 7.06 (1H, dd, J=0.7, 8.2Hz), 7.15 (1H, d, J=0.7Hz), 7.38 (1H, br-s), 7.54 (1H, br-s).

(4) Ethyl 4-chloro-7-(2-dimethylaminoethoxy)-1-methyl-2-indolecarboxylate:

^{1}H NMR (CDCl$_3$) δ: 1.39-1.44 (3H, m), 2.36 (6H, s), 2.82 (2H, t, J=5.9Hz), 4.17 (2H, t, J=5.9Hz), 4.33-4.40 (5H, m), 6.59 (1H, d, J=8.3Hz), 6.96 (1H, d, J=7.9Hz), 7.30 (1H, s).

(5) Ethyl 6-carbamoylmethoxy-1-methyl-2-indolecarboxylate:

^1H NMR ($CDCl_3$) δ: 1.38-1.43 (3H, m), 4.03 (3H, s), 4.32-4.40 (2H, m), 4.60 (2H, s), 5.61 (1H, br-s), 6.59 (1H, br-s), 6.79 (1H, d, J=2.3Hz), 6.84 (1H, dd, J=2.3, 8.6Hz), 7.26-7.27 (1H, m), 7.57-7.60 (1H, m).

(6) Ethyl 4-chloro-1-methyl-7-[2-(N-pyrrolidinyl)-ethoxy]-2-indolecarboxylate:

^1H NMR ($CDCl_3$) δ: 1.39-1.44 (3H, m), 1.79-1.84 (4H, m), 2.63-2.68 (4H, m), 2.97-3.02 (2H, m), 4.20-4.24 (2H, m), 4.33-4.41 (5H, m), 6.60 (1H, d, J=8.6Hz), 6.97 (1H, d, J=8.3 Hz), 7.31 (1H, s).

(7) Methyl 7-(3-tert-butoxycarbonylaminopropoxy)-1-methyl-2-indolecarboxylate:

^1H NMR ($CDCl_3$) δ: 1.43 (9H, s), 2.09 (2H, t, J=6.3Hz), 3.35-3.42 (2H, m), 3.89 (3H, s), 4.13-4.18 (2H, m), 4.39 (3H, s), 4.73 (1H, br-s), 6.69 (1H, d, J=7.9Hz), 6.96-7.02 (1H, m), 7.21-7.26 (2H, m).

(8) Ethyl 7-(3-tert-butoxycarbonylaminopropoxy)-4-chloro-1-methyl-2-indolecarboxylate:

^1H NMR ($CDCl_3$) δ: 1.38-1.44 (12H, m), 2.03-2.13 (2H, m), 3.33-3.40 (2H, m), 4.12 (2H, t, J=5.9Hz), 4.33-4.41 (5H, m), 4.70 (1H, br-s), 6.58 (1H, d, J=8.3Hz), 6.96 (1H, d, J=8.3Hz), 7.31 (1H, s).

(9) Ethyl 6-(3-tert-butoxycarbonylaminopropoxy)-1-methyl-2-indolecarboxylate:

^1H NMR ($CDCl_3$) δ: 1.37-1.42 (3H, m), 1.45 (9H, s), 2.02 (2H, dd, J=6.3, 12.5Hz), 3.33-3.40 (2H, m), 4.02 (3H, s), 4.10 (2H, t, J=5.9Hz), 4.35 (2H, dd, J=6.9, 14.2Hz), 4.78 (1H, br-s), 6.76 (1H, s), 6.78-6.83 (1H, m), 7.24-7.26 (1H, m), 7.53 (1H, d, J=8.6Hz).

(10) Ethyl 7-(2-tert-butoxycarbonylaminoethoxy)-4-chloro-1-methyl-2-indolecarboxylate:

^1H NMR ($CDCl_3$) δ: 1.39-1.44 (3H, m), 1.45 (9H, s), 3.63 (2H, dd, J=5.3, 10.6Hz), 4.13 (2H, t, J=5.3Hz), 4.30-4.41 (5H, m), 4.63-4.89 (1H, m), 6.58 (1H, d, J=8.3Hz), 6.97 (1H, d, J=8.3Hz), 7.31 (1H, s).

(11) Methyl 1-methyl-7-[2-(2-tetrahydropyranyl)oxyethoxy]-2-indolecarboxylate:

^1H NMR ($CDCl_3$) δ: 1.52-1.85 (6H, m), 3.50-3.58 (1H, m), 3.83-3.90 (5H, m), 4.11-4.19 (1H, m), 4.26-4.30 (2H, m), 4.42 (3H, s), 4.73-4.75 (1H, m), 6.70-6.73 (1H, m), 7.01 (1H, t, J=7.9Hz), 7.22-7.26 (2H, m).

(12) Ethyl 4-chloro-1-methyl-7-[2-(2-tetrahydropyranyl)-oxyethoxy]-2-indolecarboxylate:

^1H NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7.3Hz), 1.52-1.85 (6H, m), 3.51-3.56 (1H, m), 3.81-3.91 (2H, m), 4.10-4.17 (1H, m), 4.23-4.27 (2H, m), 4.33-4.40 (5H, m), 4.72-4.73 (1H, m), 6.61 (1H, d, J=8.2Hz), 6.96 (1H, d, J=8.3Hz), 7.30 (1H, s).

(13) Ethyl 4-chloro-7-(2:3-isopropylidenedioxypropoxy)-1-methyl-2-indolecarboxylate:

^1H NMR ($CDCl_3$) δ: 1.39-1.47 (9H, m), 3.91-3.99 (1H, m), 4.06-4.23 (3H, m), 4.33-4.41 (5H, m), 4.51-4.63 (1H, m), 6.60 (1H, d, J=8.3Hz), 6,97 (1H, d, J=8.3Hz), 7.31 (1H, s).

(14) Ethyl 4-chloro-1-methyl-7-[4-(2-tetrahydropyranyl)-oxybutoxy]-2-indolecarboxylate:

^1H NMR ($CDCl_3$) δ: 1.39-1.44 (3H, m), 1.52-1.85 (8H, m), 1.87-2.04 (2H, m), 3.44-3.55 (2H, m), 3.79-3.91 (2H, m), 4.10 (2H, t, J=6.3Hz), 4.33-4.41 (5H, m), 4.58-4.61 (1H, m), 6,56 (1H, d, J=8.3Hz), 6.96 (1H, d, J=8.3Hz), 7.30 (1H, s).

Reference Example 16

Preparation of ethyl 4-carboxy-1-methyl-2-indolecarboxylate

a) Preparation of ethyl 4-hydroxymethyl-1-methyl-2-indolecarboxylate

In a solvent mixture of 20 ml of 2N hydrochloric acid and 60 ml of tetrahydrofran was dissolved 4.00 g (12.6 mmol) of ethyl 1-methyl-4-(2-tetrahydropyranyl)-oxymethyl-2-indolecarboxylate. The solution was stirred at 50°C for an hour. The reaction mixture was poured onto ice water and the aqueous layer was extracted three times with ethyl acetate. The combined extracts were washed with saturated sodium hydrogencarbonate solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to give 2.90 g (99%) of ethyl 4-hydroxymethyl-1-methyl-2-indolecarboxylate.

b) Preparation of ethyl 4-carboxy-1-methyl-2-indolecarboxylate

In 30 ml of acetone was dissolved 0.70 g (3.00 mmols) of ethyl 4-hydroxymethyl-1-methyl-2-indolecarboxylate. After 3.3 ml of Jones' reagent, which was prepared by dissolving 26.7 g of chromium (VI) oxide in a mixture of 23 ml of conc. sulfuric acid and 40 ml of water and adding water to make the whole volume 100 ml, was added dropwise to the above solution at room temperature, the mixture was stirred at room temperature for an hour. The reaction mixture was poured onto ice water and the aqueous layer was extracted three times with chloroform. The combined extracts were washed with saturated sodium hydrogencarbonate solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to give 0.38 g (51.2%) of ethyl 4-carboxy-1-methyl-2-indo-

lecarboxylate.

^{1}H NMR (DMSO-d_6) δ: 1.34-1.40 (3H, m), 4.08 (3H, s), 4.35 (2H, dd, J=7.3, 14.2Hz), 7.41-7.47 (1H, m), 7.72 (1H, s), 7.82-7.89 (2H, m), 12.7 (0.5H, br-s).

Reference Example 17

Preparation of ethyl 6-benzyloxy-4-methyl-2-indolecarboxylate

a) Preparation of 4-benzyloxy-2-methylbenzoic acid

A mixture of 5.00 g (18.9 mmol) of 5-benzyloxy-2-bromotoluene, 0.46 g (18.9 mmol) of metallic magnesium, a catalytic amount of iodine and 20 ml of tetrahydrofuran was refluxed for 2 hours. After cooling to -50°C, carbon dioxide was bubbled into the reaction solution for 30 minutes. The reaction temperature was then elevated to room temperature and stirring was continued at the same temperature for further 2 hours. Next the reaction mixture was poured into 1N hydrochloric acid followed by extraction twice with ethyl acetate. The combined extracts were washed with water. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 1.40 g of 4-benzyloxy-2-methylbenzoic acid.

b) Preparation of methyl 4-benzyolxy-2-methylbenzoate

Using 1.40 g (5.78 mmol) of 4-benzyloxy-2-methylbenzoic acid, 1.37 g (11.6 mmol) of thionyl chloride and 50 ml of methanol, the reaction was carried out in a manner similar to Reference Example 6 to obtain 0.77 g of methyl 4-benzyloxy-2-methylbenzoate.

c) Preparation of 4-benzyloxy-2-methylbenzyl alcohol

A suspension of 0.11 g (2.93 mmol) of lithium aluminum hydride in 20 ml of tetrahydrofuran was cooled to 0°C. A solution of 0.75 g (2.93 mmol) of methyl 4-benzyloxy-2-methylbenzoate in 20 ml of tetrahydrofuran was added dropwise to the suspension at 0°C. After stirring at 0°C for 2 hours, the reaction mixture was treated in a conventional manner to give 0.66 g of 4-benzyloxy-2-methylbenzyl alcohol.

d) Preparation of 4-benzyloxy-2-methylbenzaldehyde

A mixture of 0.70 g (3.07 mmol) of 4-benzyolxy-2-methylbenzyl alcohol, 2.67 g (30.7 mmol) of manganese dioxide, 0.5 ml of methanol and 20 ml of chloroform was stirred at room temperature for 11 hours. Then insoluble matters were filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 0.60 g of 4-benzyloxy-2-methylbenzaldehyde.

e) Preparation of ethyl 3-(4-benzyloxy-2-methylphenyl)-2-azidopropenoate

The reaction was carried out in a manner similar to Reference Example 13 a) except for using 2.80 g (12.4 mmol) of 4-benzyloxy-2-methylbenzaldehyde, 6.39 g (49.5 mmol) of ethyl azidacetate, 3.37 g (49.5 mmol) of sodium ethoxide and 50 ml of ethanol. Ethyl 3-(4-benzyloxy-2-methylphenyl)-2-azidopropenoate was thus obtained in the yield of 3.24 g.

f) Preparation of ethyl 6-benzyloxy-4-methyl-2-indolecarboxylate

The reaction was carried out in a manner similar to Reference Example 13 b) except for using 3.22 g of ethyl 3-(4-benzyloxy-2-methylphenyl)-2-azido-propenoate and 100 ml of toluene. Ethyl 6-benzyloxy-4-methyl-2-indolecarboxylate was thus obtained in the yield of 2.66 g.

^{1}H NMR ($CDCl_3$) δ: 1.38-1.43 (3H, m), 2.51 (3H, s), 4.38 (2H, dd, J=6.9, 14.2Hz), 5.09 (2H, s), 6.72 (2H, s), 7.19 (1H, d, J=2.3Hz), 7.29-7.46 (5H, m), 8.71 (1H, br-s)

The following compound was prepared in a manner similar to Reference Example 17.

(1) Ethyl 6-benzyloxy-4-trifluoromethyl-2-indolecarboxylate:

^{1}H NMR ($CDCl_3$) δ: 1.39-1.44 (3H, 4.37-4.45 (2H, m), 5.14 (2H, s), 7.05 (1H, s), 7.23-7.24 (1H, m), 7.30 (1H, s), 7.35-7.47 (5H, m), 8.92 (1H, br-s)

Example 1

Preparation of 1-methyl-2-indoloylguanidine

After 8.58 g (89.8 mmol) of guanidine hydrochloride was added to 70 ml of a methanol solution of 4.85 g (89.8 mmol) of sodium methoxide, the mixture was stirred at room temperature. The precipitated sodium chloride was filtered off to obtain the solution. Then 1.70 g (8.97 mmol) of methyl 1-methyl-2-indolecarboxylate was added to the thus obtained solution. Subsequently methanol was distilled off under reduced pressure. The resulting residue was heated at 130°C for 5 minutes and then allowed to stand at room temperature for an hour. Thereafter water was poured onto the reaction solution and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with water. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was isolated and purified by silica gel column chromatography to give the desired 1-methyl-2-indoloylguanidine. The compound was dissolved in chloroform and treated with hydrogen chloride/ether. Thus 0.70 g (30.8%) of 1-methyl-2-indoloylguanidine hydrochloride was obtained.

M.P.: 250°C or higher

^{1}H NMR (DMSO-d_6) δ: 4.04 (3H, s), 7.12-7.21 (1H, m), 7.31-7.44 (1H, m), 7.61 (1H, d, J=8.6Hz), 7.73 (1H, d, J=7.9Hz), 7.89 (1H, s), 8.5 (2H, br-s), 8.7 (2H, br-s), 11.9 (1H, br-s).

Example 2

Preparation of 1-methyl-5-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 1.00 g (5.29 mmol) of methyl 1-methyl-5-indolecarboxylate, 5.05 g (52.9 mmol) of guanidine hydrochloride and 50 ml of a methanol solution of 2.85 g (52.9 mmol) of sodium methoxide. Thus 0.92 g (68.9%) of 1-methyl-5-indoloylguanidine hydrochloride was obtained.

M.P.: 260°C or higher

^{1}H NMR (DMSO-d_6) δ: 3.86 (3H, s), 6.62-6.64 (1H, m), 7.50 (1H, d, J=3.3Hz), 7.61 (1H, d, J=8.9Hz), 7.91-7.95 (1H, m), 8.44 (2H, br-s), 8.47 (1H, d, J=1.3Hz), 8.7 (2H, br-s), 11.7 (1H, br-s).

Example 3

Preparation of 1-methyl-3-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 1.00 g (5.29 mmol) of methyl 1-methyl-3-indolecarboxylate, 5.05 g (52.9 mmol) of guanidine hydrochloride and 50 ml of a methanol solution of 2.85 g (52.9 mmol) of sodium methoxide. Thus 0.48 g (35.9%) of 1-methyl-3-indoloylguanidine hydrochloride was obtained.

M.P.: 252-253°C.

^{1}H NMR (DMSO-d_6) δ: 3.91 (3H, s), 7.25-7.37 (2H, m), 7.58-7.61 (1H, m), 8.15 (1H, dd, J=1.3, 6.6Hz), 8.3 (2H, br-s), 8.6 (2H, br-s), 8.78 (1H, s), 11.8 (1H, br-s).

Example 4

Preparation of 1-methyl-4-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 0.85 g (4.49 mmol) of methyl 1-methyl-4-indolecarboxylate, 4.29 g (44.9 mmol) of guanidine hydrochloride and 50 ml of a methanol solution of 2.43 g (44.9 mmol) of sodium methoxide. Thus 0.75 g (66.1%) of 1-methyl-4-indoloylguanidine hydrochloride was obtained.

M.P.: 186-187°C.

^{1}H NMR (DMSO-d_6) δ: 3.88 (3H, s), 6.97 (1H, d, J=3.0Hz), 7.92-7.35 (1H, m), 7.56 (1H, d, J=3.0Hz), 7.84 (1H, d, J=7.9Hz), 7.98 (1H, d, J=7.6Hz), 8.5 (2H, br-s), 8.7 (2H, br-s), 11.7 (1H, br-s).

Example 5

Preparation of 4-chloro-1-methyl-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 2.00 g (8.94 mmol) of methyl 4-chloro-1-methyl-2-indolecarboxylate, 8.54 g (89.4 mmol) of guanidine hydrochloride and 50 ml of a methanol solution of 4.83 g (89.4 mmol) of sodium methoxide. Thus 1.06 g (41.3%) of 4-chloro-1-methyl-2-indoloylguanidine hydrochloride was obtained.

M.P.: 288-290°C.

^{1}H NMR (DMSO-d_6) δ: 4.05 (3H, s), 7.24 (1H, d, J=7.6Hz), 7.35-7.41 (1H, m), 7.62 (1H, d, J=8.6Hz), 7.98 (1H, s), 8.56 (2H, br-s), 8.63 (2H, br-s), 12.0 (1H, br-s).

The compounds of Examples 6 through 81 were prepared in a manner similar to Example 1.

Example 6

5-Chloro-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 43.6%, M.P.: 281-282°C

^{1}H NMR (DMSO-d_6) δ: 4.03 (3H, s), 7.39 (1H, dd, J=2.0, 8.9Hz), 7.67 (1H, d, J=8.9Hz), 7.77 (1H, s), 7.81 (1H, d, J=1.7Hz), 8.5 (2H, br-s), 8.6 (2H, br-s), 11.9 (1H, br-s).

Example 7

6-Chloro-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 59.6%, M.P.: 290-294°C

^{1}H NMR (DMSO-d_6) δ: 4.02 (3H, s), 7.17 (1H, dd, J=2.0, 8.6Hz), 7.74-7.77 (2H, m), 7.84 (1H, s), 8.5 (2H, br-s), 8.6 (2H, br-s), 11.9 (1H, br-s).

Example 8

7-Chloro-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 56.5%, M.P.: 243-244°C

^{1}H NMR (DMSO-d_6) δ: 4.33 (3H, s), 7.11-7.17 (1H, m), 7.41 (1H, d, J=7.6Hz), 7.71 (1H, d, J=7.9Hz), 7.81 (1H, s), 8.5 (2H, br-s), 8.6 (2H, br-s), 12.0 (1H, br-s).

Example 9

1,4-Dimethyl-2-indoloylguanidine hydrochloride:

Yield: 32.5%, M.P.: 279-280°C

^{1}H NMR (DMSO-d_6) δ: 2.53 (3H, s), 4.02 (3H, s), 6.96 (1H, d, J=6.9Hz), 7.26-7.32 (1H, m), 7.41 (1H, d, J=8.3Hz), 7.99 (1H, s), 8.5 (2H, br-s), 8.7 (2H, br-s), 11.9 (1H, br-s).

Example 10

1,5-Dimethyl-2-indoloylguanidine hydrochloride:

Yield: 30.5%, M.P.: 281-282°C

^{1}H NMR DMSO-d_6) δ: 2.41 (3H, s), 4.00 (3H, s), 7.23 (1H, d, J=8.9Hz), 7.48-7.51 (2H, m), 7.79 (1H, s), 8.5 (2H, br-s), 8.7 (2H, br-s), 11.9 (1H, br-s).

Example 11

1,6-Dimethyl-2-indoloylguanidine hydrochloride:

Yield: 63.1%, M.P.: 267-269°C

^{1}H NMR (DMSO-d_6) δ: 2.47 (3H, s), 3.99 (3H, s), 7.02 (1H, d, J=8.3Hz), 7.41 (1H, s), 7.61-8.00 (2H, m), 8.4 (2H, br-s), 8.5 (2H, br-s), 11.6 (1H, br-s).

Example 12

1,7-Dimethyl-2-indoloylguanidine hydrochloride:

Yield: 27.3%, M.P.: 271-273°C

^1H NMR (DMSO-d_6) δ: 2.78 (3H, s), 4.25 (3H, s), 6.99-7.11 (2H, m), 7.53 (1H, d, J=7.6Hz), 7.70 (1H, s), 8.4 (2H, br-s), 8.6 (2H, br-s), 11.8 (1H, br-s).

Example 13

5-Methoxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 50.1%, M.P.: 235-236°C

^1H NMR (DMSO-d_6) δ: 3.80 (3H, s), 4.01 (3H, s), 7.03-7.07 (1H, m), 7.16 (1H, d, J=2.3Hz), 7.52 (1H, d, J=8.9Hz), 7.75 (1H, s), 8.4 (2H, br-s), 8.7 (2H, br-s), 11.8 (1H, br-s).

Example 14

1-Methyl-6-indoloylguanidine hydrochloride:

Yield: 62.1%, M.P.: 297-298°C

^1H NMR (DMSO-d_6) δ: 3.94 (3H, s), 6.55 (1H, dd, J=0.7, 3.0Hz), 7.61 (1H, d, J=3.0Hz), 7.67-7.78 (2H, m), 8.4 (2H, br-s), 8.6 (1H, br-s), 8.9 (2H, br-s), 12.0 (1H, br-s).

Example 15

1-Benzyl-2-indoloylguanidine hydrochloride:

Yield: 54.9%, M.P.: 228-229°C

^1H NMR (DMSO-d_6) δ: 5.86 (2H, s), 7.03 (2H, d, J=6.6Hz), 7.17-7.39 (4H, m), 7.57 (1H, d, J=8.3Hz), 7.78 (1H, d, J=7.9Hz), 7.98 (1H, s), 8.4 (2H, br-s), 8.6 (2H, br-s), 11.9 (1H, br-s).

Example 16

1-Benzyl-3-indoloylguanidine hydrochloride:

Yield: 66.2%, M.P.: 252-253°C

^1H NMR (DMSO-d_6) δ: 5.53 (2H, s), 7.23-7.37 (7H, m), 7.62-7.66 (1H, m), 8.15-8.18 (1H, m), 8.3 (2H, br-s), 8.6 (2H, br-s), 8.95 (1H, s), 11.8 (1H, br-s).

Example 17

1-Isopropyl-3-indoloylguanidine hydrochloride:

Yield: 49.7%, M.P.: 221-223°C

^1H NMR (DMSO-d_6) δ: 1.51 (6H, d, J=6.6Hz), 4.85-4.90 (1H, m), 7.24-7.34 (2H, m), 7.67 (1H, d, J=7.6Hz), 8.14-8.17 (1H, m), 8.3 (2H, br-s), 8.6 (2H, br-s), 9.12 (1H, s), 11.9 (1H, br-s).

Example 18

2-Indoloylguanidine hydrochloride:

Yield: 61.9%, M.P.: 192-194°C

^1H NMR (DMSO-d_6) δ: 7.09-7.14 (1H, m), 7.28-7.34 (1H, m), 7.49 (1H, d, J=8.3Hz), 7.71 (1H, d, J=8.3Hz), 8.5 (2H, br-s), 8.7 (2H, br-s), 12.06 (1H, br-s), 12.13 (1H, br-s).

Example 19

3-Indoloylguanidine hydrochloride:

Yield: 42.2%, M.P.: 287°C

^1H NMR (DMSO-d_6) δ: 7.20-7.29 (2H, m), 7.53 (1H, dd, J=1.7, 6.6Hz), 8.12-8.16 (1H, m), 8.3 (2H, br-s), 8.7 (2H, br-s), 8.83 (1H, d, J=3.3Hz), 11.8 (1H, br-s), 12.2 (1H, br-s).

Example 20

5-Indoloylguanidine hydrochloride:

Yield: 55.9%, M.P.: 219-222°C

^1H NMR (DMSO-d_6) δ: 6.61-6.63 (1H, m), 7.50-7.56 (2H, m), 7.85-7.89 (1H, m), 8.45 (2H, br-s), 8.49

(1H, d, J=1.7Hz), 8.75 (2H, br-s), 11.6 (1H, br-s), 11.7 (1H, br-s).

Example 21

1-Isopropyl-5-indoloylguanidine hydrochloride:

Yield: 72.5%, M.P.: 219°C

^{1}H NMR (DMSO-d_6) δ: 1.48 (6H, d, J=6.6Hz), 4.81-4.88 (1H, m), 6.67 (1H, d, J=3.3Hz), 7.68-7.71 (2H, m), 7.89-7.93 (1H, m), 8.3-8.6 (3H, m), 8.7 (2H, br-s), 11.7 (1H, br-s).

Example 22

4-Methoxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 54.5%, M.P.: 281-282°C

^{1}H NMR (DMSO-d_6) δ: 3.93 (3H, s), 4.01 (3H, s), 6.62 (1H, d, J=7.9Hz), 7.16 (1H, d, J=8.6Hz), 7.30-7.36 (1H, m), 7.83 (1H, s), 8.5 (2H, br-s), 8.6 (2H, br-s), 11.7 (1H, br-s).

Example 23

6-Methoxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 75.5%, M.P.: 272°C

^{1}H NMR (DMSO-d_6) δ: 3.87 (3H, s), 4.00 (3H, s), 6.81 (1H, dd, J=2.0, 8.9Hz), 7.05 (1H, d, J=2.0Hz), 7.59 (1H, d, J=8.9Hz), 7.84 (1H, s), 8.4 (2H, br-s), 8.7 (2H, br-s), 11.8 (1H, br-s).

Example 24

1-Methyl-4-nitro-2-indoloylguanidine hydrochloride:

Yield: 97.7%, M.P.: 292-293°C

^{1}H NMR (DMSO-d_6) δ: 4.14 (3H, s), 7.59-7.65 (1H, m), 8.16 (1H, m), 8.20-8.28 (2H, m), 8.5 (4H, br-s), 11.8 (1H, br-s).

Example 25

1-Methyl-6-nitro-2-indoloylguanidine hydrochloride:

Yield: 68.4%, M.P.: 279-283°C

^{1}H NMR (DMSO-d_6) δ: 4.15 (3H, s), 7.89 (1H, s), 7.95-8.03 (2H, m), 8.51-8.66 (5H, m), 12.1 (1H, br-s).

Example 26

1-Methyl-7-nitro-2-indoloylguanidine hydrochloride:

Yield: 66.8%, M.P.: 268-270°C

^{1}H NMR (DMSO-d_6) δ: 3.83 (3H, s), 7.36 (1H, t, J=7.9Hz), 7.98 (1H, s), 8.06 (1H, dd, J=1.0, 7.9Hz), 8.19 (1H, dd, J=1.0, 7.9Hz), 8.44-8.74 (4H, m), 12.2 (1H, br-s).

Example 27

1-Methyl-5-nitro-2-indoloylguanidine hydrochloride:

Yield: 73.6%, M.P.: 294-295°C

^{1}H NMR (DMSO-d_6) δ: 4.09 (3H, s), 7.86-7.91 (2H, m), 8.23 (1H, dd, J=2.3, 9.2Hz), 8.49 (4H, br-s), 8.83 (1H, d, J=2.3Hz), 11.9 (1H, br-s).

Example 28

1-Methyl-7-indoloylguanidine hydrochloride:

Yield: 37.4%, M.P.: 203-204°C

^{1}H NMR (DMSO-d_6) δ: 3.78 (3H, s), 6.60 (1H, d, J=3.3Hz), 7.16 (1H, t, J=7.6Hz), 7.44 (1H, d, J=3.0Hz), 7.53 (1H, d, J=7.6Hz), 7.85 (1H, d, J=7.9Hz), 8.44 (2H, br-s), 8.52 (2H, br-s), 11.90 (1H, br-s).

Example 29

1-Methyl-4-trifluoromethyl-2-indoloylguanidine hydrochloride:

Yield: 57.8%, M.P.: 283-285°C

^{1}H NMR (DMSO-d_6) δ: 4.10 (3H, s), 7.52-7.58 (2H, m), 7.91 (1H, s), 7.98-8.01 (1H, m), 8.4-8.8 (4H, m), 11.99 (1H, br-s).

Example 30

5-Fluoro-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 60.8%, M.P.: 278-281°C

^{1}H NMR (DMSO-d_6) δ: 4.03 (3H, s), 7.25-7.33 (1H, m), 7.54 (1H, dd, J=2.3, 9.6Hz), 7.69 (1H, dd, J=4.6, 9.2Hz), 7.82 (1H, s), 8.51 (2H, br-s), 8.69 (2H, br-s), 11.98 (1H, br-s).

Example 31

5-Ethoxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 30.9%, M.P.: 234-236°C

^{1}H NMR (DMSO-d_6) δ: 1.35 (3H, t, J=6.9Hz), 3.99 (3H, s), 4.05 (2H, dd, J=6.9, 14.2Hz), 7.05 (1H, dd, J=2.3, 9.2Hz), 7.16 (1H, d, J=2.3Hz), 7.54 (1H, d, J=8.9Hz), 7.73 (1H, s), 8.42 (2H, br-s), 8.65 (2H, br-s), 11.81 (1H, br-s).

Example 32

5-Benzyloxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 45.2%, M.P.: 249-251°C

^{1}H NMR (DMSO-d_6) δ: 3.99 (3H, s), 5.14 (2H, s), 7.12-7.16 (1H, m), 7.28-7.58 (7H, m), 7.67 (1H, s), 8.28-8.68 (4H, m), 11.71 (1H, br-s).

Example 33

1-Methyl-6-trifluoromethyl-2-indoloylguanidine hydrochloride:

Yield: 44.4%, M.P.: 255-257°C

^{1}H NMR (DMSO-d_6) δ: 4.11 (3H, s), 7.44 (1H, dd, J=1.3, 8.6Hz), 7.97 (1H, d, J=8.6Hz), 8.10 (1H, s), 8.48 (2H, br-s), 8.63 (2H, br-s), 12.03 (1H, br-s).

Example 34

7-Benzyloxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 53.5%, M.P.: 221-222°C

^{1}H NMR (DMSO-d_6) δ: 4.27 (3H, s), 5.26 (2H, s), 6.97-7.08 (2H, m), 7.27-7.56 (5H, m), 7.72 (1H, s), 8.43 (2H, br-s), 8.60 (2H, br-s), 11.80 (1H, br-s).

Example 35

1-(2-Naphthylmethyl)-2-indoloylguanidine hydrochloride:

Yield: 56.4%, M.P.: 254-255°C

^{1}H NMR (DMSO-d_6) δ: 6.02 (2H, s), 7.17-7.27 (2H, m), 7.32-7.38 (1H, m), 7.43-7.48 (3H, m), 7.60 (1H, d, J=7.9Hz), 7.73-7.86 (4H, m), 8.07 (1H, s), 8.43 (2H, br-s), 8.67 (2H, br-s), 12.04 (1H, br-s).

Example 36

1-(2-Phenylethyl)-2-indoloylguanidine hydrochloride:

Yield: 55.1%, M.P.: 262-264°C

^{1}H NMR (DMSO-d_6) δ: 2.97-3.03 (2H, m), 4.73-4.79 (2H, m), 7.13-7.24 (6H, m), 7.32-7.38 (1H, m), 7.59 (1H, d, J=7.9Hz), 7.73 (1H, d, J=7.9Hz), 7.84 (1H, s), 8.43 (2H, br-s), 8.62 (2H, br-s), 11.78 (1H, br-s).

Example 37

1-(4-Bromobenzyl)-2-indoloylguanidine hydrochloride:

Yield: 53.3%, M.P.: 260-263°C

^{1}H NMR (DMSO-d_6) δ: 5.82 (2H, s), 6.99 (2H, d, J=8.3Hz), 7.17-7.23 (1H, m), 7.35-7.40 (1H, m), 7.47 (2H, d, J=8.3Hz), 7.57 (1H, d, J=8.3Hz), 7.79 (1H, d, J=7.9Hz), 8.06 (1H, s), 8.47 (2H, br-s), 8.69 (2H, br-s), 12.07 (1H, br-s).

Example 38

1-(4-Nitrobenzyl)-2-indoloylguanidine hydrochloride:

Yield: 42.7%, M.P.: 245-247°C

^{1}H NMR (DMSO-d_6) δ: 5.98 (2H, s), 7.20-7.27 (3H, m), 7.39 (1H, t, J=7.3Hz), 7.56 (1H, d, J=8.3Hz), 7.82 (1H, d, J=7.9Hz), 8.05 (1H, s), 8.16 (2H, d, J=8.6Hz), 8.41 (2H, br-s), 8.61 (2H, br-s), 12.02 (1H, br-s).

Example 39

1-(4-Methoxybenzyl)-2-indoloylguanidine hydrochloride:

Yield: 54.8%, M.P.: 239-240°C

^{1}H NMR (DMSO-d_6) δ: 3.68 (3H, s), 5.78 (2H, s), 6.82 (2H, d, J=8.6Hz), 7.18 (1H, t, J= 7.3Hz), 7.34-7.40 (1H, m), 7.61 (1H, d, J=8.6Hz), 7.77 (1H, d, J=7.9Hz), 7.92 (1H, s), 8.43 (2H, br-s), 8.60 (2H, br-s), 11.89 (1H, br-s).

Example 40

1-(3-Phenylpropyl)-2-indoloylguanidine hydrochloride:

Yield: 39.0%, M.P.: 147-148°C

^{1}H NMR (DMSO-d_6) δ: 1.97-2.13 (2H, m), 5.62 (2H, t, J=8.0Hz), 4.59 (2H, t, J=7.0Hz), 7.11-7.34 (6H, m), 7.40 (1H, dt, J=1.0, 8.0Hz), 7.57 (1H, d, J=8.0Hz), 7.76 (1H, d, J=8.0Hz), 7.81 (1H, s), 8.25-8.70 (4H, m), 11.75 (1H, br-s).

Example 41

1-(4-Phenylbutyl)-2-indoloylguanidine hydrochloride:

Yield: 51.0%, M.P.: 154-155°C

^{1}H NMR (DMSO-d_6) δ: 1.43-1.65 (2H, m), 1.65-1.68 (2H, m), 2.57 (2H, t, J=8.0Hz), 4.58 (1H, t, J=7.0Hz), 7.03-7.32 (6H, m), 7.39 (1H, dt, J= 1.0, 8.0Hz), 7.63 (1H, d, J=8.0Hz), 7.73 (1H, d, J=8.0Hz), 7.92 (1H, s), 8.20-9.00 (4H, m), 11.95 (1H, br-s).

Example 42

1-Isopropyl-6-indoloylguanidine hydrochloride:

Yield: 37.7%, M.P.: 218-220°C

^{1}H NMR (DMSO-d_6) δ: 1.51 (6H, d, J=6.6Hz), 4.92-5.02 (1H, m), 6.59 (1H, d, J=3.0Hz), 7.66-7.81 (3H, m), 8.41 (2H, br-s), 8.66 (1H, s), 8.86 (2H, br-s), 12.04 (1H, br-s).

Example 43

1-Benzyl-6-indoloylguanidine hydrochloride:

Yield: 44.5%, M.P.: 227-228°C

^{1}H NMR (DMSO-d_6) δ: 5.57 (2H, s), 6.62 (1H, d, J=3.0Hz), 7.24-7.32 (5H, m), 7.69-7.79 (2H, m), 7.81 (1H, d, J=3.0Hz), 8.43 (2H, br-s), 8.71 (1H, s), 8.86 (2H, br-s), 12.06 (1H, br-s).

Example 44

1-Isopropyl-4-indoloylguanidine hydrochloride:

Yield: 49.0%, M.P.: 95-97°C

^{1}H NMR (DMSO-d_6) δ: 1.48 (6H, d, J=6.6Hz), 4.87 (1H, m), 7.01 (1H, d, J=3.0Hz), 7.26-7.31 (1H, m),

7.72 (1H, d, J=3.3Hz), 7.91 (1H, d, J=8.3Hz), 8.02 (1H, d, J=7.6Hz), 8.54 (2H, br-s), 8.83 (2H, br-s), 11.85 (1H, br-s).

Example 45

1-Benzyl-4-indoloylguanidine hydrochloride:

Yield: 42.6%, M.P.: 203-205°C

^{1}H NMR (DMSO-d_6) δ: 5.52 (2H, s), 7.03 (1H, d, J=3.0Hz), 7.17-7.32 (6H, m), 7.74 (1H, t, J=1.7Hz), 7.84 (1H, d, J=7.9Hz), 7.98 (1H, d, J=7.6Hz), 8.48 (2H, br-s), 8.77 (2H, br-s), 11.79 (1H, br-s).

Example 46

4-Benzyloxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 57.6%, M.P.: 260°C

^{1}H NMR (DMSO-d_6) δ: 4.01 (3H, s), 5.26 (2H, s), 6.75 (1H, d, J=7.6Hz), 7.20 (1H, d, J=8.6Hz), 7.30-7.54 (6H, m), 7.75 (1H, s), 8.40 (4H, br-s), 11.41 (1H, br-s).

Example 47

1,3-Dimethyl-2-indoloylguanidine hydrochloride:

Yield: 55.5%, M.P.: 228-229°C

^{1}H NMR (DMSO-d_6) δ: 2.56 (3H, s), 3.84 (3H, s), 7.12-7.18 (1H, m), 7.34-7.40 (1H, m), 7.53 (1H, d, J=8.3Hz), 7.69 (1H, d, J=7.9Hz), 8.61-8.68 (4H, m), 11.67 (1H, br-s).

Example 48

1-Methyl-7-phenyl-2-indoloylguanidine hydrochloride:

Yield: 58.9%, M.P.: 265-267°C

^{1}H NMR (DMSO-d_6) δ: 4.07 (3H, s), 7.27 (1H, d, J=7.3Hz), 7.41-7.75 (7H, m), 7.89 (1H, s), 8.50 (4H, br-s), 11.77 (1H, br-s).

Example 49

4-Acetyl-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 45.4%, M.P.: 288-289°C

^{1}H NMR (DMSO-d_6) δ: 2.71 (3H, s), 4.07 (3H, s), 7.50-7.56 (1H, m), 7.91-7.97 (2H, m), 8.25 (1H, s), 8.53 (4H, br-s), 11.71 (1H, br-s).

Example 50

6-Benzyloxy-1-methyl-2-indoloylguanidine hydrochloride :

Yield: 42.7%, M.P.: 269-270°C

^{1}H NMR (DMSO-d_6) δ: 3.99 (3H, s), 5.20 (2H, s), 6.89 (1H, d, J=10.6Hz), 7.22 (1H, s), 7.35-7.58 (6H, m), 7.62-7.67 (1H, m), 8.4 (4H, br-s), 11.35 (1H, br-s).

Example 51

4-Ethoxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 69.8%, M.P.: 262-263°C

^{1}H NMR (DMSO-d_6) δ: 1.42 (3H, t, J=6.9Hz), 3.99 (3H, s), 4.19 (2H, q, J=6.9Hz), 6.62 (1H, d, J=7.6Hz), 7.16 (1H, d, J=8.6Hz), 7.28-7.34 (1H, m), 7.77 (1H, s), 8.51 (4H, br-s), 11.60 (1H, br-s).

Example 52

1-(2-Carbamoylethyl)-2-indoloylguanidine hydrochloride:

Yield: 30.0%, M.P.: 285-286°C

^{1}H NMR (DMSO-d_6) δ: 2.55 (2H, t, J=7.3Hz), 4.74 (2H, t, J=7.3Hz), 6.85 (1H, br-s), 7.17 (1H, t, J=6.9Hz), 7.33 (1H, br-s), 7.39 (1H, ddd, J=1.0, 7.3, 7.8Hz), 7.70 (2H, dd, J=8.4, 17.7Hz), 7.82 (1H, s), 8.46 (2H, br-s),

8.64 (2H, br-s), 11.85 (1H, br-s).

Example 53

1-Propyl-2-indoloylguanidine hydrochloride:

Yield: 53.2%, M.P.: 218-219°C

^{1}H NMR (DMSO-d_6) δ: 0.85 (3H, t, J=7.6Hz), 1.66-1.77 (2H, m), 4.51 (2H, dd, J=6.9, 7.6Hz), 7.10-7.23 (1H, m), 7.32-7.45 (1H, m), 7.65 (1H, d, J=8.6Hz), 7.73 (1H, d, J=7.9Hz), 7.97 (1H, s), 8.52 (2H, br-s), 8.77 (2H, br-s), 12.01 (1H, br-s).

Example 54

1-(2-Methoxyethyl)-2-indoloylguanidine hydrochloride:

Yield: 15.0%, M.P.: 174-176°C

^{1}H NMR (DMSO-d_6) δ: 3.16 (3H, s), 3.63 (2H, t, J=5.3Hz), 4.72 (2H, t, J=5.3Hz), 7.11-7.22 (1H, m), 7.31-7.44 (1H, m), 7.66 (1H, d, J=8.6Hz), 7.72 (1H, d, J=7.9Hz), 7.89 (1H, s), 8.49 (2H, br-s), 8.70 (2H, br-s), 11.96 (1H, br-s).

Example 55

4-Fluoro-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 53.1%, M.P.: 281-282°C

^{1}H NMR (DMSO-d_6) δ: 4.04 (3H, s), 6.97 (1H, dd, J=7.6, 10.2Hz), 7.35-7.43 (1H, m), 7.50 (1H, d, J=8.3Hz), 7.89 (1H, s), 8.48-8.60 (4H, m), 11.92 (1H, br-s).

Example 56

4-Bromo-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 58.2%, M.P.: 306-307°C

^{1}H NMR (DMSO-d_6) δ: 4.04 (3H, s), 7.30-7.36 (1H, m), 7.42 (1H, d, J=7.6Hz), 7.69 (1H, d, J=8.6Hz), 7.78 (1H, s), 8.56 (4H br-s), 11.91 (1H, br-s).

Example 57

4-Isobutyloxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 58.1%, M.P.: 245-247°C

^{1}H NMR (DMSO-d_6) δ: 1.05 (6H, d, J=6.9Hz), 2.06-2.16 (1H, m), 3.90 (2H, d, J=6.3Hz), 3.99 (3H, s), 6.61 (1H, d, J=7.9Hz), 7.16 (1H, d, J=8.6Hz), 7.28-7.34 (1H, m), 7.84 (1H, s), 8.51 (4H, br-s), 11.65 (1H, br-s).

Example 58

4-Isopropoxy-1-methy1-2-indoloylguanidine hydrochloride:

Yield: 62.3% M.P.: 269-270°C

^{1}H NMR (DMSO-d_6) δ: 1.35 (6H, d, J=5.9Hz), 3.99 (3H, s), 4.75-4.84 (1H, m), 6.65 (1H, d, J=7.6Hz), 7.14 (1H, d, J=8.6Hz), 7.28-7.34 (1H, m), 7.75 (1H, s), 8.53 (4H, br-s), 11.59 (1H, br-s).

Example 59

1-Methyl-7-(2-phenylethoxy)-2-indoloylguanidine hydrochloride:

Yield: 24.3%, M.P.: 155-156°C

^{1}H NMR (DMSO-d_6) δ: 3.21 (2H, t, J=6.3Hz), 4.13 (3H, s), 4.43 (2H, t, J=6.3Hz), 6.95 (1H, d, J=7.9Hz), 7.08 (1H, t, J=7.9Hz), 7.25-7.44 (6H, m), 7.60 (1H, s), 8.44 (4H, br-s), 11.62 (1H, br-s).

Example 60

1-Methyl-7-(3-phenylpropoxy)-2-indoloylguanidine hydrochloride:

Yield: 46.1%, M.P.: 165-166°C

^1H NMR (DMSO-d_6) δ: 2.12-2.17 (2H, m), 2.79-2.85 (2H, m), 4.09-4.13 (2H, m), 4.31 (3H, s), 6.83 (1H, m), 7.00-7.05 (1H, m), 7.19-7.32 (6H, m), 7.67 (1H, s), 8.56 (4H, br-s), 11.75 (1H, br-s).

Example 61

7-Benzyloxy-4-chloro-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 54.4%, M.P.: 264°C

^1H NMR (DMSO-d_6) δ: 4.27 (3H, s), 5.26 (2H, s), 6.96 (1H, d, J=8.6Hz), 7.11 (1H, d, J=8.3Hz), 7.32-7.54 (5H, m), 7.78 (1H, s), 8.5-8.6 (4H, m), 11.94 (1H, br-s).

Example 62

4-Carboxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 40.5%, M.P.: 302-303°C

^1H NMR (DMSO-d_6) δ: 4.07 (3H, s), 7.48-7.54 (1H, m), 7.86-7.95 (2H, m), 8.10 (1H, s), 8.3-8.7 (4H, m), 11.58 (1H, br-s), 13.0 (0.7H, br-s).

Example 63

7-Carbamoylmethoxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 56.7%, M.P.: 268-269°C

^1H NMR (DMSO-d_6) δ: 4.32 (3H, s), 4.61 (2H, s), 6.76 (1H, d, J=7.9Hz), 7.03 (1H, t, J=7.9Hz), 7.30 (1H, d, J=7.6Hz), 7.40 (1H, br-s), 7.58 (1H, br-s), 7.68 (1H, s), 8.54 (4H, m), 11.74 (1H, br-s).

Example 64

7-Carbamoylmethoxy-4-chloro-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 29.7%, M.P.: 270-271°C

^1H NMR (DMSO-d_6) δ: 4.33 (3H, s), 4.61 (2H, s), 6.73 (1H, d, J=8.3Hz), 7.10 (1H, d, J=8.3Hz), 7.39 (1H, br-s), 7.58 (1H, br-s), 7.74 (1H, s), 8.57 (4H, br-s), 11.93 (1H, br-s).

Example 65

4-Chloro-7-(2-dimethylaminoethoxy)-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 50.8%, M.P.: 287-288°C

^1H NMR (DMSO-d_6) δ: 2.86 (6H, d, J=5.0Hz), 3.62-3.64 (2H, m), 4.29 (3H, s), 4.51-4.55 (2H, m), 6.92 (1H, d, J=8.2Hz), 7.14 (1H, d, J=8.3Hz), 7.88 (1H, s), 8.6-8.9 (4H, m), 11.01 (1H, br-s), 12.13 (1H, br-s).

Example 66

6-Carbamoylmethoxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 26.8%, M.P.: 275°C

^1H NMR (DMSO-d_6) δ: 3.98 (3H, s), 4.53 (2H, s), 6.90-6.95 (1H, m), 7.11 (1H, d, J=2.0Hz), 7.45 (1H, br-s), 7.58 (1H, br-s), 7.65 (1H, d, J=8.9Hz), 7.77 (1H, s), 8.38-8.58 (4H, m), 11.72 (1H, br-s).

Example 67

1-Methyl-6-(2-phenylethoxy)-2-indoloylguanidine hydrochloride:

Yield: 48.6%, M.P.: 219-221°C

^1H NMR (DMSO-d_6) δ: 3.07-3.12 (2H, m), 3.97 (3H, s), 4.29 (2H, t, J=6.9Hz), 6.79-6.83 (1H, m), 7.11 (1H, d, J=2.0Hz), 7.23-7.39 (5H, m), 7.60 (1H, d, J=8.6Hz), 7.74 (1H, s), 8.36-8.56 (4H, m), 11.67 (1H, br-s).

Example 68

1-Methyl-6-(3-phenylpropoxy)-2-indoloylguanidine hydrochloride:

Yield: 72.4%, M.P.: 232-233°C

^1H NMR (DMSO-d_6) δ: 2.02-2.13 (2H, m), 2.75-2.81 (2H, m), 3.97 (3H, s), 4.07 (2H, t, J=6.3Hz), 6.82-6.86 (1H, m), 7.06 (1H, d, J=1.7Hz), 7.16-7.33 (5H, m), 7.61 (1H, d, J=8.9Hz), 7.75 (1H, s), 8.36-8.58 (4H, m),

11.69 (1H, br-s).

Example 69

1-Methyl-6-methylsulfonyl-2-indoloylguanidine hydrochloride:

Yield: 30.7%, M.P.: 303-304°C

^{1}H NMR (DMSO-d_6) δ: 3.25 (3H, s), 4.12 (3H, s), 7.65 (1H, dd, J=1.3, 8.6Hz), 7.97-8.00 (2H, m), 8.24 (1H, s), 8.57 (2H, br-s), 8.74 (2H, br-s), 12.23 (1H, br-s).

Example 70

1-Methyl-4-methylsulfonyl-2-indoloylguanidine hydrochloride:

Yield: 19.4%, M.P.: 313-314°C

^{1}H NMR (DMSO-d_6) δ: 3.30 (3H, s), 4.10 (3H, s), 7.60 (1H, dd, J=7.6, 8.3Hz), 7.72-7.75 (1H, m), 8.04-8.07 (2H, m), 8.63 (4H, br-s), 12.29 (1H, br-s).

Example 71

4-Chloro-1-(2-methoxyethyl)-2-indoloylguanidine hydrochloride:

Yield: 27.0%, M.P.: 147-150°C

^{1}H NMR (DMSO-d_6) δ: 3.15 (3H, s), 3.63 (2H, t, J=5.3Hz), 4.73 (2H, t, J=5.3Hz), 7.26 (1H, d, J=6.9Hz), 7.31-7.44 (1H, m), 7.66 (1H, d, J=8.6Hz), 7.94 (1H, s), 8.60 (2H, br-s), 8.67 (2H, br-s), 12.05 (1H, br-s).

Example 72

1-(2-carbamoylethyl)-4-chloro-2-indoloylguanidine hydrochloride:

Yield: 11.0%, M.P.: 295°C

^{1}H NMR (DMSO-d_6) δ:2.56 (2H, t, J=6.9Hz), 4.76 (2H, t, J=6.9Hz), 6.84 (1H, br-s), 7.26 (1H, d, J=7.7Hz), 7.30-7.46 (2H, m), 7.68 (1H, d, J=8.2Hz), 7.89 (1H, s), 8.56 (2H, br-s), 8.62 (2H, br-s), 11.95 (1H, br-s).

Example 73

4-Chloro-1-methyl-7-[2-(N-pyrrolidinyl)ethoxy]-2-indoloylguanidine hydrochloride:

Yield: 53.8%, M.P.: 250°C

^{1}H NMR (DMSO-d_6) δ: 1.93-2.03 (4H, m), 3.0-3.2 (2H, m), 3.61-3.71 (4H, m), 4.30 (3H, s), 4.51-4.54 (2H, m), 6.92 (1H, d, J=8.2Hz), 7.14 (1H, d, J=8.3Hz), 7.85 (1H, s), 8.6-8.7 (4H, m), 11.20 (1H, br-s), 12.07 (1H, br-s).

Example 74

4-Chloro-7-(3-dimethylaminopropoxy)-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 35.4%, M.P.: 250°C

^{1}H NMR (DMSO-d_6) δ: 2.24-2.30 (2H, m), 2.78 (6H, s), 3.2-3.3 (2H, m), 4.20 (2H, t, J=5.9Hz), 4.29 (3H, s), 6.85 (1H, d, J=8.3Hz), 7.11 (1H, d, J=8.3Hz), 7.82 (1H, s), 8.5-8.7 (4H, m), 10.74 (1H, br-s), 12.04 (1H, br-s).

Example 75

7-[2-(N-Benzyl-N-methylamino)ethoxy]-4-chloro-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 43.5%, M.P.: 230°C

^{1}H NMR (DMSO-d_6) δ: 2.80 (3H, s), 3.61 (2H, br-s), 4.20 (3H, s), 4.40-4.57 (4H, m), 6.89 (1H, d, J=8.3Hz), 7.13 (1H, d, J=8.3Hz), 7.45-7.47 (3H, m), 7.6-7.7 (2H, m), 7.82 (1H, s), 8.5-8.7 (4H, m), 11.10 (1H, br-s), 12.04 (1H, br-s).

Example 76

4-Isopropenyl-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 41.5%, M.P.: 235°C

^{1}H NMR (DMSO-d_6) δ: 2.24 (3H, s), 4.03 (3H, s), 5.35-5.36 (1H, m), 5.48 (1H, d, J=1.0Hz), 7.15 (1H, dd, J=0.7, 7.3Hz), 7.38 (1H, dd, J=7.3, 8.6Hz), 7.56 (1H, d, J=8.6Hz), 8.07 (1H, s), 8.45-8.70 (4H, m), 12.03 (1H, br-s).

Example 77

4-Isopropenyl-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 75.6%, M.P.: 255°C

^{1}H NMR (DMSO-d_6) δ: 1.35 (6H, d, J=6.9Hz), 3.27-3.37 (1H, m), 4.02 (3H, s), 7.03 (1H, d, J=6.9Hz), 7.31-7.37 (1H, m), 7.44 (1H, d, J=8.6Hz), 8.08 (1H, s), 8.42-8.70 (4H, m), 11.97 (1H, br-s).

Example 78

1-(2-Diethylaminoethyl)-2-indoloylguanidine hydrochloride:

Yield: 19.3%, M.P.: 250°C

^{1}H NMR (DMSO-d_6) δ: 1.28 (6H, t, J=7.3Hz), 3.10-3.43 (6H, m), 4.88-5.10 (2H, m), 7.23 (1H, t, J=7.6Hz), 7.46 (1H, ddd, J=1.0, 8.3, 8.7Hz), 7.76 (1H, d, J=7.6Hz), 7.94 (1H, d, J=8.7Hz), 8.09 (1H, br-s), 8.61 (2H, br-s), 8.79 (2H, br-s), 11.27 (1H, br-s), 12.3 (1H, br-s).

Example 79

4-Chloro-1-(2-diethylaminoethyl)-2-indoloylguanidine hydrochloride:

Yield: 36.0%, M.P.: 260-261°C

^{1}H NMR (DMSO-d_6) δ: 1.28 (6H, t, J=7.3Hz), 3.10-3.48 (6H, m), 4.90-5.15 (2H, m), 7.31 (1H, d, J=7.7Hz), 7.45 (1H, dd, J=7.7, 8.3Hz), 7.98 (1H, d, J=8.3Hz), 8.14 (1H, br-s), 8.72 (2H, br-s), 8.75 (2H, br-s), 11.38 (1H, br-s), 12.33 (1H, br-s).

Example 80

1-(2-Dimethylaminoethyl)-2-indoloylguanidine hydrochloride:

Yield: 27.0%, M.P.: 239-242°C

^{1}H NMR (DMSO-d_6) δ: 2.84 (6H, s), 3.23-3.53 (2H, m), 4.85-5.08 (2H, m), 7.23 (1H, dd, J=7.3, 7.9Hz), 7.41-7.43 (1H, m), 7.77 (1H, d, J=7.9Hz), 7.88 (1H, d, J=8.3Hz), 8.11 (1H, s), 8.64 (2H, br-s), 8.81 (2H, br-s), 11.09 (1H, br-s), 12.26 (1H, br-s).

Example 81

4-Chloro-1-(2-dimethylaminoethyl)-2-indoloylguanidine hydrochloride:

Yield: 26.0%, M.P.: 245-248°C

^{1}H NMR (DMSO-d_6) δ: 2.84 (6H, s), 3.31-3.52 (2H, m), 4.88-5.08 (2H, m), 7.32 (1H, d, J=7.6Hz), 7.46 (1H, dd, J=7.6, 8.3Hz), 7.91 (1H, d, J=8.3Hz), 8.16 (1H, s), 8.71 (2H, br-s), 8.77 (2H, br-s), 11.19 (1H, m), 12.32 (1H, br-s).

Example 82

Preparation of 1-benzyl-5-indoloylguanidine

After 2.24 g (23.4 mmol) of guanidine hydrochloride was added to 50 ml of a methanol solution of 1.26 g (23.4 mmol) of sodium methoxide, 0.80 g (2.34 mmol) of benzyl 1-benzyl-5-indolecarboxylate was added to the resulting mixture. The mixture was then stirred for 30 hours while heating at 50 to 60°C. Methanol was distilled off under reduced pressure and the residue was purified by silica gel column chromatography followed by treatment with 2N hydrochloric acid to give 0.08 g (10.4%) of 1-benzyl-5-indoloylguanidine hydrochloride.

M.P.: 216-222°C

^{1}H NMR (DMSO-d_6) δ: 5.51 (2H, s), 6.69 (1H, d, J=2.6Hz), 7.20-7.34 (5H, m), 7.62-7.68 (2H, m), 7.88 (1H, dd, J=1.7, 8.9Hz), 8.43-8.48 (3H, m), 8.72 (2H, br-s), 11.7 (1H, br-s).

Example 83

Preparation of 7-methoxy-1-methyl-2-indoloylguanidine hydrochloride

a) The reaction was carried out in a manner similar to Reference Example 1-a) except for using 24.6 g (0.20 mmol) of 2-methoxyaniline, 15.2 g (0.22 mol) of sodium nitrite, 84 ml of conc. hydrochloric acid, 28.8 g (0.20 mmol) of ethyl 2-methylacetacetate and 20 ml of ethanol. Crude ethyl 2-(2-methoxyphenylhydrazono)-propionate was obtained in an amount of 23.0 g.

b) After 23.0 g of the crude ethyl 2-(2-methoxyphenylhydrazono)propionate obtained above was added to 150 ml of 10% hydrogen chloride/ethanol, the mixture was refluxed for 30 minutes. After cooling, the reaction mixture was poured onto ice water and the mixture was extracted three times with ether. After washing with water and then with aqueous sodium bicarbonate solution, the extract was dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure. The resulting residue was roughly purified by silica gel column chromatography to give 8.00 g of crude ethyl 7-methoxy-2-indolecarboxylate.

c) The reaction was carried out in a manner similar to Reference Example 5 except for using 8.00 g (36.5 mmol) of the crude ethyl 7-methoxy-2-indolecarboxylate obtained above, 1.44 g (36 mmol) of 60% sodium hydride, 7.76 g (54.7 mmol) of methyl iodide and 50 ml of dimethylformamide. Thus 4.4 g of crude ethyl 7-methoxy-1-methyl-2-indolecarboxylate was obtained.

d) The reaction was carried out in a manner similar to Example 1 except for using 4.40 g (18.9 mmol) of the crude ethyl 7-methoxy-1-methyl-2-indole-carboxylate obtained above, 18.0 g (189 mmol) of guanidine hydrochloride and 150 ml of a methanol solution of 10.2 g (189 mmol) of sodium methoxide. Thus 1.58 g of 7-methoxy-1-methyl-2-indoloylguanidine hydrochloride was obtained; yield: 5.6%, based on 2-methoxyaniline.

M.P.: 252-253°C

^{1}H NMR (DMSO-d_6) δ: 3.93 (3H, s), 4.28 (3H, s), 6.86 (1H, d, J=7.6Hz), 7.05 (1H, t, J=7.9Hz), 7.26 (1H, d, J=7.6Hz), 7.74 (1H, s), 8.5 (2H, br-s), 8.6 (2H, br-s), 11.8 (1H, br-s).

Example 84

Preparation of 1-isopropyl-2-indoloylguanidine

A tetrahydrofuran solution, 60 ml, containing 2.00 g (9.84 mmol) of 1-isopropyl-2-indolecarboxylic acid and 2.39 g (14.8 mmol) of carbonyldiimidazole was stirred at room temperature for 2 hours and then at 45 to 50°C for an hour. After cooling to room temperature, 30 ml of a dimethylformamide solution of 5.64 g (59.0 mmol) of guanidine hydrochloride and 5.97 g (59.0 mmol) of triethylamine was added to the reaction mixture followed by stirring at room temperature for 12 hours. The mixture was then distilled off under reduced pressure and water was added to the resulting residue. After adjusting pH in the range of 5 to 6 with 2N hydrochloric acid, the mixture was extracted three times with ethyl acetate. After drying over anhydrous magnesium sulfate, the extract was acidified with hydrogen chloride/ether. The precipitated crystals were filtered and dried to give 1.31 g (47.4%) of the desired 1-isopropyl-2-indoloyl-guanidine hydrochloride.

M.P.: 150-151°C

^{1}H NMR (DMSO-d_6) δ: 1.61 (6H, d, J=7.3Hz), 5.46-5.57 (1H, m), 7.15 (1H, t, J=7.9Hz), 7.32-7.38 (1H, m), 7.68-7.78 (3H, m), 8.5 (2H, br-s), 8.7 (2H, br-s), 11.8-11.9 (1H, m).

The reaction was carried out in a manner similar to Example 84 to obtain the compound of Example 85.

Example 85

1-Carbamoylmethyl-2-indoloylguanidine hydrochloride:

Yield: 2.1%, M.P.: 261-262°C

^{1}H NMR (DMSO-d_6) δ: 5.17 (2H, s), 7.10-7.28 (2H, m), 7.32-7.45 (1H, m), 7.56 (1H, d, J=8.6Hz), 7.59 (1H, br-s), 7.75 (1H, dd, J=0.7, 7.0Hz), 7.81 (1H, s), 8.45 (2H, br-s), 8.61 (2H, br-s), 11.90 (1H, br-s).

Example 86

Preparation of 5-chloro-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 84 except for using 2.00 g (10.2 mmol) of 5-

chloro-2-indolecarboxylic acid, 1.82 g (11.3 mmol) of carbonyldiimidazole, 5.86 g (61.3 mmol) of guanidine hydrochloride, 6.20 g (61.3 mmol) of triethylamine, 50 ml of tetrahydrofuran and 50 ml of dimethylformamide. Thus 1.85 g (66.2%) of 5-chloro-2-indoloylguanidine hydrochloride was obtained.

M.P.: 250°C or higher

^{1}H NMR (DMSO-d_6) δ: 7.32 (1H, dd, J=2.0, 8.9Hz), 7.51 (1H, d, J=8.9Hz), 7.82 (2H, s), 8.53 (2H, br-s), 8.68 (2H, br-s), 12.2 (1H, br-s), 12.3 (1H, br-s).

Example 87

Preparation of 6-amino-1-methyl-2-indoloylguanidine

After 1.10 g (4.21 mmol) of 1-methyl-6-nitro-2- indoloylguanidine was dissolved in a solvent mixture of 100 ml of tetrahydrofuran and 100 ml of methanol, 0.50 g of 10% palladium/carbon was added to the solution at room temperature in a nitrogen flow, while stirring. Catalytic hydrogenation was then performed at ambient temperature under normal pressure. After completion of the reaction, the catalyst was filtered off and the filtrate was then concentrated under reduced pressure. Hydrogen chloride/methanol was added to the resulting residue to convert the compound into the hydrochloride, whereby 0.73 g (64.7%) of 6-amino-1-methyl-2-indoloyl-guanidine hydrochloride was obtained.

M.P.: 282-283°C

^{1}H NMR (DMSO-d_6) δ: 4.00 (3H, s), 7.06 (1H, dd, J=1.7, 8.6Hz), 7.39 (1H, s), 7.76 (1H, d, J=8.6Hz), 7.93 (1H, s), 8.5 (2H, br-s), 8.7 (2H, br-s), 9.0-10.3 (2H, br), 12.0 (1H, br-s).

The reaction was carried out in a manner similar to Example 87 to prepare the compounds of Examples 88 through 90 shown below.

Example 88

4-Amino-1-methyl-2-indoloylguanidine hydrochloride:

Yield: >99%, M.P.: 279-283°C

^{1}H NMR (DMSO-d_6) δ: 4.00 (3H, s), 6.80 (1H, d, J=7.6Hz), 7.20-7.31 (2H, m), 7.84 (1H, s), 8.5 (2H, br-s), 8.6 (2H, br-s), 11.9 (1H, br-s).

Example 89

5-Amino-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 89.8%, M.P.: 301-302°C

^{1}H NMR (DMSO-d_6) δ: 4.04 (3H, s), 7.35-7.39 (1H, m), 7.72-7.79 (2H, m), 7.93 (1H, s), 8.5 (2H, br-s), 8.7 (2H, br-s), 10.1 (2H, br-s), 12.1 (1H, br).

Example 90

7-Amino-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 66.7%, M.P.: 299-300°C

^{1}H NMR (DMSO-d_6) δ: 4.28 (3H, s), 7.08-7.14 (1H, m), 7.24 (1H, d, J=7.3Hz), 7.55 (1H, d, J=7.9Hz), 7.76 (1H, s), 8.5 (2H, br-s), 8.6 (2H, br-s), 12.0 (1H, br-s).

Example 91

Preparation of 5-hydroxy-1-methyl-2-indoloylguanidine

In 50 ml of methanol was dissolved 0.83 g (2.58 mmol) of 5-benzyloxy-1-methyl-2-indoloylguanidine obtained in Example 32. While stirring at room temperature, 0.30 g of 10% palladium/carbon was added to the solution in a nitrogen flow and catalytic hydrogenation was then conducted at ambient temperature under normal pressure. After completion of the reaction, the catalyst was filtered off and the filtrate was then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 5-hydroxy-1-methyl-2-indoloylguanidine. The 5-hydroxy-1-methyl-2-indoloylguanidine was further treated with hydrogen chloride/methanol to give 0.37 g (68.6%) of 5-hydroxy-1-methyl-2-indoloylguanidine hydrochloride.

M.P.: 288-289°C

^1H NMR (DMSO-d_6) δ: 3.96 (3H, s), 6.93-6.98 (2H, m), 7.43-7.47 (1H, m), 7.65 (1H, s), 8.43 (2H, br-s), 8.65 (2H, br-s), 9.18 (1H, s), 11.76 (1H, br-s).

The reaction was carried out in a manner similar to Example 91 to prepare the compounds of Examples 92 through 96 shown below.

Example 92

7-Hydroxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 53.0%, M.P.: 244-246°C

^1H NMR (DMSO-d_6) δ: 4.29 (3H, s), 6.71 (1H, d, J=7.6Hz), 6.88-6.94 (1H, m), 7.12 (1H, d, J=7.9Hz), 7.65 (1H, s), 8.42-8.56 (4H, m), 10.08 (1H, s), 11.70 (1H, br-s).

Example 93

4-Hydroxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 27.4%, M.P.: 267-268°C

^1H NMR (DMSO-d_6) δ: 3.96 (3H, s), 6.50 (1H, d, J=7.6Hz), 7.00 (1H, d, J=8.3Hz), 7.16-7.22 (1H, m), 7.71 (1H, s), 8.42 (4H, br-s), 10.14 (1H, br-s), 11.51 (1H, br-s).

Example 94

6-Hydroxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 73.4%, M.P.: 270-271°C

^1H NMR (DMSO-d_6) δ: 3.90 (3H, s), 6.72-6.76 (1H, m), 6.81 (1H, s), 7.53-7.61 (2H, m), 8.4 (4H, br-s), 9.76 (1H, br-s), 11.39 (1H, br-s).

Example 95

4-Chloro-7-hydroxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 23.9%, M.P.: 280°C

^1H NMR (DMSO-d_6) δ: 4.30 (3H, s), 6.70 (1H, d, J=7.9Hz), 6.96 (1H, d, J=8.3Hz), 7.68 (1H, s), 8.54 (4H, br-s), 10.37 (1H, s), 11.79 (1H, br-s).

Example 96

4-Chloro-6-hydroxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 40.1%, M.P.: 270°C

^1H NMR (DMSO-d_6) δ: 3.91 (3H, s), 6.83-6.84 (2H, m), 7.77 (1H, s), 8.3-8.7 (4H, m), 10.14 (1H, s), 11.72 (1H, br-s).

Example 97

Preparation of 4-acetamido-1-methyl-2-indoloylguanidine

a) Preparation of ethyl 4-amino-1-methyl-2-indolecarboxylate

In a solvent mixture of 50 ml of tetrahydrofuran and 50 ml of methanol was dissolved 1.37 g (5.52 mmol) of ethyl 1-methyl-4-nitro-2-indole-carboxylate. Thereafter 0.30 g of 10% palladium/carbon was added to the solution and catalytic hydrogenation was then conducted at ambient temperature under normal pressure. After completion of the reaction, the catalyst was filtered off and the filtrate was then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 1.2 g (>99%) of ethyl 4-amino-1-methyl-2-indolecarboxylate.

b) Preparation of ethyl-4-acetamido-1-methyl-2-indolecarboxylate

In 20 ml of pyridine was dissolved 1.2 g (5.52 mmol) of ethyl 4-amino-1-methyl-2-indolecarboxylate. While stirring at room temperature, 10 ml of anhydrous acetic acid was added to the solution. After stirring for 2 hours at room temperature, the reaction mixture was poured onto ice water. The mixture was extracted three times

with ethyl acetate. The combined extracts were washed with 1N hydrochloric acid and then with saturated sodium hydrogencarbonate solution. The solvent was then distilled off under reduced pressure and the residue was purified by silica gel column chromatography to give 1.40 g (97.9%) of ethyl 4-acetamido-1-methyl-2-indolecarboxylate.

c) Preparation of 4-acetamido-1-methyl-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 1.40 g (5.38 mmol) of ethyl 4-acetamido-1-methyl-2-indole-carboxylate, 5.14 g (53.8 mmol) of guanidine hydrochloride and 50 ml of a methanol solution of 2.91 g (53.8 mmol) of sodium methoxide. Thus 1.15 g (69.0%) of 4-acetamido-1-methyl-2-indoloylguanidine hydrochloride was obtained.

M.P.: 277-279°C

^{1}H NMR (DMSO-d_6) δ: 2.15 (3H, s), 3.99 (3H, s), 7.30-7.35 (2H, m), 7.5-7.6 (1H, m), 7.79 (1H, s), 8.4-8.7 (4H, m), 10.00 (1H, br-s), 11.68 (1H, br-s).

The reaction was carried out in a manner similar to Example 97 to prepare the compounds of Examples 98 through 100 shown below.

Example 98

5-Acetamido-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 49.2%, M.P.: 260-261°C

^{1}H NMR (DMSO-d_6) δ: 2.06 (3H, s), 3.99 (3H, s), 7.46 (1H, dd, J=2.0, 8.9Hz), 7.56 (1H, d, J=8.9Hz), 7.83 (1H, s), 8.09 (1H, d, J=1.7Hz), 8.47 (2H, br-s), 8.71 (2H, br-s), 9.97 (1H, br-s), 11.92 (1H, br-s).

Example 99

7-Acetamido-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 17.1%, M.P.: 285°C

^{1}H NMR (DMSO-d_6) δ: 2.10 (3H, s), 4.07 (3H, s), 7.07-7.15 (2H, m), 7.61-7.64 (1H, m), 7.76 (1H, s), 8.45 (2H, br-s), 8.60 (2H, br-s), 9.90 (1H, br-s), 11.86 (1H, br-s).

Example 100

6-Acetamido-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 63.8%, M.P.: 280-281°C

^{1}H NMR (DMSO-d_6) δ: 2.09 (3H, s), 3.95 (3H, s), 7.18 (1H, dd, J=1.7, 8.6Hz), 7.64 (1H, d, J=8.9Hz), 7.72 (1H, s), 8.09 (1H, s), 8.2-8.8 (4H, m), 10.17 (1H, br-s), 11.75 (1H, br-s).

Example 101

Preparation of 1-hydroxy-2-indoloylguanidine

a) Preparation of methyl 1-hydroxy-2-indolecarboxylate

The reaction was carried out in a manner similar to Reference Example 6 except for using 3.99 g (22.5 mmol) of 1-hydroxy-2-indolecarboxylic acid, 5.36 g (45.0 mmol) of thionyl chloride and 100 ml of methanol. Thus 2.56 g (59.5%) of methyl 1-hydroxy-2-indolecarboxylate was obtained.

b) Preparation of 1-hydroxy-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 1.00 g (5.23 mmol) of methyl 1-hydroxy-2-indolecarboxylate, 5.00 g (52.3 mmol) of guanidine hydrochloride and 50 ml of a methanol solution of 2.82 g (52.3 mmol) of sodium methoxide. 1-Hydroxy-2-indoloylguanidine hydrochloride was obtained in an amount of 0.56 g (42.0%).

M.P.: 217°C

^{1}H NMR (DMSO-d_6) δ: 7.13-7.19 (1H, m), 7.37-7.52 (2H, m), 7.69-7.73 (1H, m), 8.45 (2H, br-s), 8.70 (2H, br-s), 11.4-11.8 (2H, m).

Example 102

Preparation of 1-methoxy-2-indoloylguanidine

a) Preparation of methyl 1-methoxy-2-indolecarboxylate

In a nitrogen flow 0.56 g (2.93 mmol) of methyl 1-hydroxy-2-indolecarboxylate was added to a suspension of 0.12 g (2.93 mmol) of 60% sodium hydride in 20 ml of tetrahydrofuran at room temperature. After it was confirmed that the reaction mixture became transparent, 0.83 g (5.86 mmol) of methyl iodide was added to the reaction mixture. The mixture was then refluxed for 2 hours. After cooling to room temperature, the reaction mixture was poured onto ice water followed by extraction three times with ethyl acetate. The combined extracts were washed with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 0.46 g (76.5%) of methyl 1-methoxy-2-indolecarboxylate.

b) Preparation of 1-methoxy-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 0.46 g (2.24 mmol) of methyl 1-methoxy-2-indolecarboxylate, 2.14 g (22.4 mmol) of guanidine hydrochloride and 15 ml of a methanol solution of 1.21 g (22.4 mmol) of sodium methoxide. Thus 0.15 g (24.9%) of 1-methoxy-2-indoloylguanidine hydrochloride was obtained.

M.P.: 214°C

^{1}H NMR (DMSO-d_6) δ: 4.16 (3H, s), 7.21-7.26 (1H, m), 7.44-7.50 (1H, m), 7.62 (1H, d, J=8.6Hz), 7.74-7.79 (2H, m), 8.48 (2H, br-s), 8.66 (2H, br-s), 11.93 (1H, br-s).

Example 103

Preparation of 5-benzamido-1-methyl-2-indoloylguanidine

a) Preparation of ethyl-5-benzamido-1-methyl-2-indolecarboxylate

In 20 ml of pyridine was dissolved 0.80 g (3.67 mmol) of ethyl 5-amino-1-methyl-2-indole-carboxylate. While stirring at room temperature, 0.57 g (4.03 mmol) of benzoyl chloride was added to the solution. After stirring for 2 hours at 70°C, the reaction mixture was cooled to room temperature and then poured onto ice water. The mixture was then extracted three times with ethyl acetate. The combined extracts were washed with 1N hydrochloric acid and then with saturated sodium hydrogencarbonate solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to give 0.62 g (52.5%) of ethyl 5-benzamido-1-methyl-2-indole-carboxylate.

b) Preparation of 5-benzamido-1-methyl-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 0.62 g (1.92 mmol) of ethyl 5-benzamido-1-methyl-2-indole-carboxylate, 3.68 g (38.4 mmol) of guanidine hydrochloride and 50 ml of a methanol solution of 2.08 g (38.4 mmol) of sodium methoxide. 5-Benzamido-1-methyl-2-indoloylguanidine hydrochloride was obtained in an amount of 0.38 g (53.1%).

M.P.: 185-190°C

^{1}H NMR (DMSO-d_6) δ: 4.03 (3H, s), 7.50-7.60 (4H, m), 7.63-7.74 (1H, m), 7.81 (1H, s), 7.96-8.00 (2H, m), 8.25 (1H, d, J=1.7Hz), 8.44 (2H, br-s), 8.62 (2H, br-s), 10.26 (1H, br-s), 11.82 (1H, br-s).

The reaction was carried out in a manner similar to Example 103 to prepare the compounds of Examples 104 through 106 shown below.

Example 104

4-Benzamido-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 54.7%, M.P.: 302-303°C

^{1}H NMR (DMSO-d_6) δ: 4.04 (3H, s), 7.37-7.64 (6H, m), 7.87 (1H, s), 8.05-8.09 (2H, m), 8.52 (4H, br-s), 10.35 (1H, br-s), 11.70 (1H, br-s).

Example 105

7-Benzamido-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 45.7%, M.P.: 318-319°C

^{1}H NMR (DMSO-d_6) δ: 4.07 (3H, s), 7.16-7.24 (2H, m), 7.53-7.72 (4H, m), 7.80 (1H, m), 8.04-8.06 (2H, m), 8.45 (2H, br-s), 8.61 (2H, br-s), 10.44 (1H, br-s), 11.88 (1H, br-s).

Example 106

6-Benzamido-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 40.1%, M.P.: 309°C

^{1}H NMR (DMSO-d_6) δ: 4.00 (3H, s), 7.48-7.62 (4H, m), 7.70-7.75 (2H, m), 7.98-8.01 (2H, m), 8.27 (1H, s), 8.2-8.8 (4H, m), 10.45 (1H, br-s), 11.73 (1H, br-s).

Example 107

Preparation of 1-(4-aminobenzyl)-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 87 except for using 0.45 g (1.20 mmol) of 1-(4-nitrobenzyl)-2-indoloylguanidine, 0.50 g of 10% palladium/carbon, 25 ml of tetrahydrofuran and 25 ml of methanol. Thus 0.33 g (79.7%) of 1-(4-amino-benzyl)-2-indoloylguanidine hydrochloride was obtained.

M.P.: 226-228°C

^{1}H NMR (DMSO-d_6) δ: 5.83 (2H, s), 7.00-7.13 (4H, m), 7.17-7.23 (1H, m), 7.34-7.40 (1H, m), 7.58 (1H, d, J=8.3Hz), 7.79 (1H, d, J=7.9Hz), 8.02 (1H, s), 8.50 (2H, br-s), 8.66 (2H, br-s), 9.0-9.8 (2H, m), 12.01 (1H, br-s).

Example 108

Preparation of 1-(2-hydroxyethyl)-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 1.00 g (3.30 mmol) of methyl 1-[2-(2-tetrahydropyranyl)oxyethyl]-2-indolecarboxylate, 3.15 g (33.0 mmol) of guanidine hydrochloride and a methanol solution of 1.78 g (33.0 mmol) of sodium methoxide. 1-[2-(2-Tetrahydropyranyl)-oxyethyl]-2-indoloylguanidine was obtained in an amount of 0.85 g. Thereafter 0.69 g of the thus obtained compound was dissolved in hydrochloric acid/methanol. The solution was stirred at room temperature for 5.5 hours. The reaction mixture was concentrated under reduced pressure and a solvent mixture of methanol and diethyl ether was added to the resulting residue. The precipitates formed were filtered and dried under reduced pressure to give 0.49 g (65%) of 1-(2-hydroxyethyl)-2-indoloylguanidine hydrochloride.

M.P.: 190-193°C

^{1}H NMR (DMSO-d_6) δ: 3.60-3.82 (2H, m), 4.60 (2H, t, J=5.0Hz), 4.74-4.97 (1H, br-s), 7.17 (1H, dt, J=7.0, 7.8Hz), 7.38 (1H, dt, J=7.0, 7.8Hz), 7.66 (1H, d, J=8.0Hz), 7.72 (1H, d, J=8.0Hz), 7.84 (1H, s), 8.20-8.90 (4H, m), 11.87 (1H, br-s).

The reaction was carried out in a manner similar to Example 108 to prepare the compounds of Examples 109 and 110 shown below.

Example 109

1-(3-Hydroxypropyl)-2-indoloylguanidine hydrochloride:

Yield: 81.0%, M.P.: 206-207°C

^{1}H NMR (DMSO-d_6) δ: 1.90 (2H, dt, J=6.9, 7.3Hz), 3.39 (2H, t, J=6.3Hz), 4.60 (2H, t, J=6.9Hz), 7.18 (1H, dd, J=7.0, 7.8Hz), 7.41 (1H, dd, J=7.1, 8.5Hz), 7.65 (1H, d, J=8.2Hz), 7.74 (1H, d, J=7.8Hz), 7.88 (1H, s), 8.28-8.85 (4H, m), 11.87 (1H, br-s).

Example 110

1-(4-Hydroxybutyl)-2-indoloylguanidine hydrochloride:

Yield: 84.0%, M.P.: 226°C

^{1}H NMR (DMSO-d_6) δ: 1.30-1.50 (2H, m), 1.62-1.86 (2H, m), 3.38 (2H, t, J=6.4Hz), 4.43 (1H, br-s), 4.56

(2H, t, J=7.3Hz), 7.17 (1H, t, J=7.4Hz), 7.40 (1H, ddd, J=1.0, 6.9, 7.4Hz), 7.65 (1H, d, J=8.3Hz), 7.73 (1H, d, J=7.9Hz), 7.96 (1H, s), 8.52 (2H, br-s), 8.76 (2H, br-s), 12.00 (1H, s).

Example 111

Preparation of 3-methyl-2-indoloylguanidine

a) Preparation of ethyl 2-phenylhydrazonobutyronate

Ethyl 2-Phenylhydrazonobutyronate was obtained in a manner similar to Reference Example 1 a) except that aniline and ethyl 2-ethylacetacetate were used in place of o-chloroaniline and ethyl 2-methylacetacetate.

b) Preparation of ethyl 3-methyl-2-indolecarboxylate

After 25.0 g of ethyl 2-henylhydrazonobutyronate was dissolved in 80 ml of hydrochloric acid/methanol, the solution was refluxed for an hour. After cooling to room temperature, the reaction mixture was poured onto ice water. The mixture was then extracted three times with diethyl ether. The combined extracts were washed with water and next with saturated sodium hydrogen-carbonate solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 14.0 g (69.0%) of ethyl 3-methyl-2-indolecarboxylate.

c) Preparation of 3-methyl-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 1.50 g (7.38 mmol) of ethyl 3-methyl-2-indolecarboxylate, 7.05 g (73.8 mmol) of guanidine hydrochloride and 50 ml of a methanol solution of 3.99 g (73.8 mmol) of sodium methoxide. Thus 1.61 g (86.3%) of 3-methyl-2-indoloylguanidine hydrochloride.

M.P.: 285-286°C

^{1}H NMR (DMSO-d_6) δ: 2.60 (3H, s), 7.12 (1H, t, J=7.9Hz), 7.31-7.44 (2H, m), 7.70 (1H, d, J=7.9Hz), 8.46 (4H, br-s), 11.78 (1H, br-s), 11.94 (1H, br-s).

Example 112

Preparation of 1-methyl-7-(3-phenylpropionamido)-2-indoloylguanidine

a) Preparation of ethyl 1-methyl-7-(3-phenylpropionamido)-2-indolecarboxylate

A suspension of 0.20 g (0.92 mmol) of ethyl 7-amino-1-methyl-2-indolecarboxylate, 0.14 g (0.94 mmol) of 3-phenylpropionic acid, 0.11 g (0.94 mmol) of 4-dimethylaminopyridine and 0.19 g (0.94 mmol) of dicyclohexylcarbodiimide in 5 ml of methylene chloride was stirred at room temperature for 24 hours. The reaction solution was poured onto ice water and the resulting mixture was extracted three times with ethyl acetate. The combined extracts were washed with 1N hydrochloric acid and next with 5% sodium hydrogencarbonate solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography to give ethyl 1-methyl 7-(3-phenylpropionamido)-2-indolecarboxylate.

b) Preparation of 1-methyl-7-(3-phenylpropionamido)-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 0.42 g (1.21 mmol) of ethyl 1-methyl-7-(3-phenylpropionamido)-2-indole-carboxylate, 2.31 g (24.2 mmols) of guanidine hydrochloride and a solution of 1.31 g (24.2 mmols) of sodium methoxide in 30 ml of methanol. 1-Methyl-7-(3-phenylpropionamido)-2-indoloylguanidine hydrochloride was obtained in an amount of 0.16 g (34.9%).

M.P.: 279-280°C

^{1}H NMR (DMSO-d_6) δ: 2.72 (2H, t, J=7.6Hz), 2.96 (2H, t, J=7.6Hz), 3.34 (3H, s), 7.03-7.14 (2H, m), 7.20-7.24 (1H, m), 7.29-7.31 (4H, m), 7.62 (1H, d, J=6.9Hz), 7.69 (1H, s), 8.53 (4H, m), 9.89 (1H, s), 11.76 (1H, br-s).

The compound of Example 113 was prepared in a manner similar to Example 112.

Example 113

1-Methyl-6-(3-phenylpropionamido)-2-indoloylguanidine hydrochloride:

Yield: 34.6%, M.P.: 245-247°C

^{1}H NMR (DMSO-d_6) δ: 2.66-2.71 (2H, m), 2.91-2.97 (2H, m), 2.91-2.97 (2H, m), 3.95 (3H, s), 7.16-7.30 (6H, m), 7.63-7.71 (2H, m), 8.13 (1H, s), 8.36-8.52 (4H, m), 10.16 (1H, br-s), 11.67 (1H, br-s).

Example 114

Preparation of 1-(3-aminopropyl)-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 1.50 g (4.51 mmol) of methyl 1-(3-tert-butoxycarbonylaminopropyl)-2-indolecarboxylate, 4.31 g (45.1 mmol) of guanidine hydrochloride and 60 ml of a methanol solution of 2.44 g (45.1 mmol) of sodium methoxide. 1-(3-tert-Butoxycarbonylaminopropyl)-2-indoloylguanidine hydrochloride was obtained in an amount of 1.57 g. After 1.55 g of the compound was dissolved in hydrochloric acid/methanol, the solution was stirred at 70°C for 3.5 hours. The reaction mixture was concentrated under reduced pressure. The resulting residue was recrystallized from water to give 0.65 g (46.0%) of 1-(3-aminopropyl)-2-indoloylguanidine hydrochloride.

M.P.: 296-297°C

^{1}H NMR (DMSO-d_6) δ: 2.05 (2H, ddd, J=7.6, 11.4, 14.5Hz), 2.63-2.86 (2H, m), 4.65 (2H, t, J=7.3Hz), 7.19 (1H, t, J=7.9Hz), 7.42 (1H, t, J=7.6Hz), 7.74 (2H, d, J=8.6Hz), 7.83-8.16 (4H, m), 8.27-9.03 (4H, m), 12.00-12.30 (1H, br-s).

The compound of Example 115 was prepared in a manner similar to Example 114.

Example 115

1-(2-Aminoethyl)-2-indoloylguanidine hydrochloride:

Yield: 54.0%, M.P.: 240°C

^{1}H NMR (DMSO-d_6) δ: 3.14-3.30 (2H, m), 4.77 (2H, t, J=6.3Hz), 7.22 (1H, dd, J=7.3, 7.6Hz), 7.45 (1H, dd, J=7.3, 7.6Hz), 7.77 (1H, d, J=7.6Hz), 7.83 (1H, d, J=7.6Hz), 8.03 (1H, br-s), 8.20 (3H, br-s), 8.58 (2H, br-s), 8.74 (2H, br-s), 12.14 (1H, br-s).

Example 116

Preparation of 4-aminomethyl-1-methyl-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 1.40 g (4.21 mmol) of ethyl 1-methyl-4-tert-butyloxycarbonylaminomethyl-2-indolecarboxylate, 4.02 g (42.1 mmol) of guanidine hydrochloride and 60 ml of a methanol solution of 2.27 g (42.1 mmol) of sodium methoxide. 1-Methyl-4-tert-butyloxycarbonylaminomethyl-2-indoloylguanidine hydrochloride was obtained in an amount of 1.50 g. After the compound was dissolved in 35 ml of trifluoroacetic acid and 70 ml of methylene chloride, the solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Thereafter ice water was poured onto the resulting residue and the aqueous layer was rendered alkaline with 28% aqueous ammonia. The mixture was then extracted three times with ethyl acetate. The combined extracts were washed with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was converted with hydrogen chloride/ether into the hydrochloride. Thus 0.58 g (43.2%) of 4-aminomethyl-1-methyl-2-indoloyl-guanidine hydrochloride was obtained.

M.P.: 283-284°C

^{1}H NMR (DMSO-d_6) δ: 4.06 (3H, s), 4.28 (2H, d, J=6.6Hz), 7.32 (1H, d, J=6.9Hz), 7.43-7.49 (1H, m), 7.66 (1H, d, J=8.3Hz), 8.28 (1H, s), 8.5-8.7 (5H, m), 8.79 (2H, br-s), 12.28 (1H, br-s).

The following compounds of Examples 117 to 122 were prepared in a manner similar to Example 116.

Example 117

7-(3-Aminopropoxy)-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 51.8%, M.P.: 287-288°C

^{1}H NMR (DMSO-d_6) δ: 2.09-2.17 (2H, m), 3.32 (2H, br-s), 4.21 (2H, t, J=5.9Hz), 4.28 (3H, s), 6.86 (1H,

d, J=6.9Hz), 7.05 (1H, t, J=7.9Hz), 7.28 (1H, d, J=7.9Hz), 7.76 (1H, s), 7.98 (3H, br-s), 8.47-8.67 (4H, m), 11.92 (1H, br-s).

Example 118

7-(3-Aminopropoxy)-4-chloro-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 41.7%, M.P.: 299-300°C

^{1}H NMR (DMSO-d_6) δ: 2.14-2.19 (2H, m), 3.00-3.02 (2H, m), 4.21-4.26 (2H, m), 4.28 (3H, s), 6.83 (1H, d, J=8.3Hz), 7.10 (1H, d, J=8.3Hz), 7.88 (1H, s), 8.18 (3H, br-s), 8.6-8.7 (4H, m), 12.12 (1H, br-s).

Example 119

6-(3-Aminopropoxy)-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 61.3%, M.P.: 280-281°C

^{1}H NMR (DMS0-d_6) δ: 2.09-2.16 (2H, m), 3.01 (2H, t, J=6.3Hz), 4.02 (3H, s), 4.19-4.24 (2H, m), 6.87 (1H, dd, J=2.0, 8.9Hz), 7.15 (1H, s), 7.75 (1H, d, J=8.9Hz), 7.95 (1H, s), 8.07 (3H, br-s), 8.51-8.80 (4H, m), 12.00 (1H, br-s).

Example 120

1-(3-Aminopropyl)-4-chloro-2-indoloylguanidine hydrochloride:

Yield: 46.0%, M.P.: 280-282°C

^{1}H NMR (DMSO-d_6) δ: 1.95-2.16 (2H, m), 2.65-2.88 (2H, m), 4.66 (2H, t, J=6.6Hz), 7.29 (1H, d, J=7.6Hz), 7.42 (1H, dd, J=7.6, 8.3Hz), 7.79 (1H, d, J=3.0Hz), 8.02 (3H, br-s), 8.11 (1H, s), 8.68 (2H, br-s), 8.78 (2H, br-s), 12.2 (1H, br-s).

Example 121

7-(2-Aminoethoxy)-4-chloro-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 31.9%, M.P.: 285°C

^{1}H NMR (DMSO-d_6) δ: 3.2-3.4 (2H, m), 4.30 (3H, s), 4.33-4.37 (2H, m), 6.89 (1H, d, J=8.3Hz), 7.13 (1H, d, J=8.3Hz), 7.83 (1H, s), 8.33 (3H, br-s), 8.6-8.7 (4H, m), 12.06 (1H, br-s).

Example 122

6-(3-Aminopropoxy)-4-chloro-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 38.7%, M.P.: 230°C

^{1}H NMR (DMSO-d_6) δ: 2.06-2.11 (2H, m), 2.97-2.99 (2H, m), 4.00 (3H, s), 4.18-4.23 (2H, m), 6.96 (1H, d, J=1.7Hz), 7.14 (1H, s), 7.95 (1H, s), 8.09 (3H, br-s), 8.5-8.7 (4H, m), 12.03 (1H, br-s).

Example 123

Synthesis of 4-hydroxymethyl-1-methyl-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 1.50 g (4.73 mmol) of ethyl 1-methyl-4-(2-tetrahydropyranyl)oxymethyl-2-indolecarboxylate, 6.02 g (63.0 mmol) of guanidine hydrochloride and a solution of 3.40 g (63.0 mmol) of sodium methoxide in 60 ml of methanol. 1-Methyl-4-(2-tetrahydropyranyl)oxymethyl-2-indoloylguanidine was obtained. After the compound was dissolved in a mixture of 30 ml of 2N hydrochloric acid and 60 ml of tetrahydrofuran, the mixture was stirred at room temperature for an hour. The reaction mixture was poured onto ice water and the aqueous layer was rendered alkaline with 28% aqueous ammonia. The mixture was then extracted three times with ethyl acetate. The combined extracts were washed with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography to give 4-hydroxymethyl-1-methyl-2-indoloylguanidine. Next, the compound was treated with hydrogen chloride/methanol to convert into the hydrochloride. 4-Hydroxymethyl-1-methyl-2-indoloyl-guanidine hydrochloride was thus obtained in an amount of 0.58 g (44.2%).

M.P.: 226-229°C

^{1}H NMR (DMSO-d_6) δ: 4.03 (3H, s), 4.80 (2H, s), 5.26 (1H, br-s), 7.17 (1H, d, J=6.9Hz), 7.34-7.39 (1H,

m), 7.48 (1H, d, J=8.3Hz), 7.93 (1H, s), 8.48-8.60 (4H, m), 11.81 (1H, br-s).

The following compounds of Examples 124 to 133 were prepared in a manner similar to Example 123.

Example 124

7-(2-Hydroxyethoxy)-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 62.5%, M.P.: 243-244°C

^{1}H NMR (DMSO-d_6) δ: 3.82 (2H, br-s), 4.12-4.15 (2H, m), 4.31 (3H, s), 4.94 (1H, br-s), 6.86 (1H, d, J=7.3Hz), 7.03 (1H, t, J=7.9Hz), 7.26 (1H, d, J=7.3Hz), 7.73 (1H, s), 8.45-8.63 (4H, m), 11.82 (1H, br-s).

Example 125

4-Chloro-7-(2-hydroxyethoxy)-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 17.7%, M.P.: 277-279°C

^{1}H NMR (DMSO-d_6) δ: 3.79-3.83 (2H, m), 4.12-4.15 (2H, m), 4.31 (3H, s), 4.9 (1H, br-s), 6.85 (1H, d, J=8.3Hz), 7.10 (1H, d, J=8.3Hz), 7.75 (1H, s), 8.58 (4H, br-s), 11.88 (1H, br-s).

Example 126

6-(2-Hydroxyethoxy)-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 59.8%, M.P.: 265-268°C

^{1}H NMR (DMSO-d_6) δ: 3.32-3.77 (2H, m), 3.98 (3H, s), 4.08-4.11 (2H, m), 4.91 (2H, m), 4.91 (1H, br-s), 6.81-6.85 (1H, m), 7.08 (1H, s), 7.61 (1H, d, J=8.9Hz), 7.81 (1H, s), 8.39-8.64 (4H, m), 11.77 (1H, br-s).

Example 127

4-Chloro-7-(2,3-dihydroxypropoxy)-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 40.2%, M.P.: 237-238°C

^{1}H NMR (DMSO-d_6) δ: 3.50 (2H, t, J=5.9Hz), 3.88-3.91 (1H, m), 4.03 (1H, dd, J=5.6, 9.9Hz), 4.15 (1H, dd, J=4.0, 9.9Hz), 4.30 (3H, s), 6.85 (1H, d, J=8.3Hz), 7.11 (1H, d, J=8.3Hz), 7.68 (1H, s), 8.50 (4H, br-s), 11.76 (1H, br-s).

Example 128

4-Chloro-7-(3-hydroxypropoxy)-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 53.2%, M.P.: 210-212°C

^{1}H NMR (DMSO-d_6) δ: 1.93-2.02 (2H, m), 3.60-3.64 (2H, m), 4.15-4.20 (2H, m), 4.28 (3H, s), 6.84 (1H, d, J=8.6Hz), 7.09 (1H, d, J=8.3Hz), 7.77 (1H, s), 8.5-8.6 (4H, m), 11.92 (1H, br-s).

Example 129

4-Chloro-7-(4-hydroxybutoxy)-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 69.5%, M.P.: 220-222°C

^{1}H NMR (DMSO-d_6) δ: 1.59-1.67 (2H, m), 1.84-1.89 (2H, m), 3.45-3.50 (2H, m), 4.10-4.15 (2H, m), 4.29 (3H, s), 6.84 (1H, d, J=8.3Hz), 7.10 (1H, d, J=8.3Hz), 7.10 (1H, d, J=8.3Hz), 7.71 (1H, s), 8.52 (4H, br-s), 11.80 (1H, br-s).

Example 130

4-Chloro-1-(3-hydroxypropyl)-2-indoloylguanidine hydrochloride:

Yield: 60.0%, M.P.: 213-215°C

^{1}H NMR (DMSO-d_6) δ: 1.78-1.98 (2H, m), 3.30-3.45 (2H, m), 4.61 (2H, t, J=7.3Hz), 4.68 (1H, br-s), 7.27 (1H, d, J=7.6Hz), 7.39 (1H, dd, J=7.3, 8.6Hz), 7.66 (1H, d, J=8.6Hz), 7.93 (1H, s), 8.55 (2H, br-s), 8.64 (2H, br-s), 11.96 (1H, br-s).

Example 131

4-Chloro-1-(4-hydroxybutyl)-2-indoloylguanidine hydrochloride:

Yield: 48.0%, M.P.: 226-227°C

^{1}H NMR (DMSO-d_6) δ: 1.28-1.51 (2H, m), 1.60-1.84 (2H, m), 3.37 (2H, t, J=6.6Hz), 4.44 (1H, br-s), 4.58 (1H, t, J=7.3Hz), 7.28 (1H, d, J=7.6Hz), 7.39 (1H, dd, J=7.6, 8.6Hz), 7.68 (1H, d, J=8.6Hz), 7.92 (1H, s), 8.53 (2H, br-s), 8.63 (2H, br-s), 11.92 (1H, br-s).

Example 132

4-Chloro-6-(2-hydroxyethoxy)-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 51.9%, M.P.: 250-252°C

^{1}H NMR (DMSO-d_6) δ: 3.74-3.77 (2H, m), 3.99 (3H, s), 4.11 (2H, t, J=5.0Hz), 6.94 (1H, d, J=2.0Hz), 7.13 (1H, s), 7.80 (1H, s), 8.3-8.7 (4H, m), 11.76 (1H, br-s).

Example 133

1-(3,4-Dihydroxybutyl)-2-indoloylguanidine hydrochloride:

Yield: 73.0%, M.P.: 219-222°C

^{1}H NMR (DMSO-d_6) δ: 1.53-1.73 (1H, m), 1.85-2.04 (1H, m), 3.12-3.55 (3H, m), 4.37-4.88 (4H, m), 7.18 (1H, t, J=7.3Hz), 7.40 (1H, ddd, J=1.0, 7.3, 7.8Hz), 7.65 (1H, d, J=8.3Hz), 7.74 (1H, d, J=7.9Hz), 7.86 (1H, s), 8.21 (2H, br-s), 8.67 (2H, br-s), 11.87 (1H, br-s).

Example 134

Preparation of 1-(2-carboxyethyl)-2-indoloylguanidine

After 0.80 g (2.23 mmol) of 1-[2-[1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl)]ethyl]-2-indoloylguanidine was suspended in 80 ml of 1,2-dimethoxyethane, 8 ml of 1N hydrochloric acid was added to the suspension. The mixture was stirred at room temperature for 20 minutes. Subsequently 10 ml of 4N sodium hydroxide solution was added to the mixture followed by stirring at room temperature for 40 minutes. Then 10 ml of 4N hydrochloric acid was added to the mixture followed by stirring at room temperature for an hour. The reaction mixture was concentrated under reduced pressure. After the resulting residue was washed with water, water was filtered off. The filtered matter was recrystallized from 0.5 N hydrochloric acid to give 0.44 g (64.0%) of 1-(2-carboxyethyl)-2-indoloyl-guanidine hydrochloride.

M.P.: 254°C

^{1}H NMR (DMSO-d_6) δ: 2.72 (2H, t, J=7.3Hz), 4.76 (2H, t, J=7.4Hz), 7.17 (1H, t, J=7.9Hz), 7.40 (1H, ddd, J=1.0, 6.9, 7.4Hz), 7.68 (1H, d, J=8.6Hz), 7.73 (1H, d, J=7.9Hz), 7.91 (1H, s), 8.50 (2H, br-s), 8.72 (2H, br-s), 12.22 (1.5H, br-s).

Example 135

Preparation of 7-carboxymethoxy-4-chloro-1-methyl-2-indoloylguanidine

A suspension of 0.40 g (1.11 mmol) of 7-carbamoylmethoxy-4-chloro-1-methyl-2-indoloylguanidine obtained in Example 64 in 100 ml of 2N hydrochloric acid was refluxed for an hour. The reaction mixture was gradually cooled. The precipitated crystals were filtered and dried under reduced pressure to give 0.39 g (97.2%) of 7-carboxymethoxy-4-chloro-1-methyl-2-indoloylguanidine hydrochloride.

M.P.: 283-284°C

^{1}H NMR (DMSO-d_6) δ: 4.34 (3H, s), 4.84 (2H, s), 6.82 (1H, d, J=8.3Hz), 7.09 (1H, d, J=8.3Hz), 7.69 (1H, s), 8.48 (4H, br-s), 11.5-13.5 (1.3H, br-s).

The following compounds of Examples 136 and 137 were prepared in a manner similar to Example 135.

Example 136

7-Carboxymethoxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 41.5%, M.P.: 264°C

^{1}H NMR (DMSO-d_6) δ: 4.34 (3H, s), 4.84 (2H, s), 6.83 (1H, d, J=7.6Hz), 7.03 (1H, t, J=7.9Hz), 7.30 (1H, d, J=7.9Hz), 7.74 (1H, s), 8.47-8.63 (4H, m), 11.71-12.07 (1H, m), 12.6-13.3 (1H, m).

Example 137

6-Carboxymethoxy-1-methyl-2-indoloylguanidine hydrochloride:

Yield: 53.0%, M.P.: 298°C

^{1}H NMR (DMSO-d_6) δ: 3.97 (3H, s), 4.79 (2H, s), 6.85 (1H, dd, J=2.0, 8.9Hz), 7.09 (1H, s), 7.63 (1H, t, J=8.9Hz), 7.72 (1H, s), 8.34-8.51 (4H, m), 10-13 (2H, m).

Example 138

Preparation of 1-methyl-7-(2-phenylethylamino)-2-indoloyl-guanidine

a) Preparation of ethyl 1-methyl-7-(2-phenylethylamino)-2-indolecarboxylate

A mixture of 0.10 g (0.46 mmol) of ethyl 7-amino-1-methyl-2-indolecarboxylate, 0.12 g (0.50 mmol) of phenylacetaldehyde as 50% isopropanol solution, 0.043 g (0.69 mmol) of sodium cyanogen borohydride and 0.1 ml of acetic acid in 5 ml of acetonitrile was stirred at room temperature for 15 minutes. Thereafter 0.2 ml of acetic acid was added to the reaction mixture. The resulting mixture was allowed to stand at room temperature for 15 hours. After 1N sodium hydroxide solution was added to the reaction mixture, the mixture was extracted three times with diethyl ether. The combined extracts were then washed with 1N potassium hydroxide solution. After drying over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to give 0.045 g (30.5%) of ethyl 1-methyl-7-(2-phenylethylamino)-2-indole-carboxylate.

b) Preparation of 1-methyl-7-(2-phenylethylamino)-2-indoloylguanidine

A mixture of 0.16 g (0.51 mmol) of ethyl 1-methyl-7-(2-phenylethylamino)-2-indolecarboxylate, 0.49 g (5.09 mmol) of guanidine hydrochloride and 0.28 g (5.09 mmol) of sodium methoxide in 10 ml of methanol was reacted in a manner similar to Example 1 to give 0.075 g (39.5%) of 1-methyl-7-(2-phenylethylamino)-2-indoloylguanidine hydrochloride.

M.P.: 220-223°C

^{1}H NMR (DMSOd_6) δ: 2.96-3.02 (2H, m), 3.29-3.35 (2H, m), 4.18 (3H, s), 6.60-6.95 (1H, m), 6.99 (1H, d, J=7.3Hz), 7.06 (1H, d, J=7.3Hz), 7.20-7.25 (1H, m), 7.31-7.33 (4H, m), 7.64 (1H, s), 8.42-8.59 (4H, m), 11.73 (1H, br-s).

The reaction was carried out in a manner similar to Example 138 to prepare the compound of Example 139.

Example 139

1-Methyl-6-(2-phenylethylamino)-2-indoloylguanidine hydrochloride:

Yield: 26.6%, M.P.: 243-246°C

^{1}H NMR (DMSO-d_6) δ: 2.91-2.97 (2H, m), 3.38-3.51 (2H, m), 3.92 (3H, s), 6.70 (1H, s), 6.79 (1H, d, J=7.9Hz), 7.20-7.29 (1H, m), 7.31 (4H, m), 7.49 (1H, d, J=8.6Hz), 7.76 (1H, s), 8.35-8.63 (4H, m), 11.64 (1H, br-s).

Example 140

Preparation of 1-(3-aminopropyl)-4-trifluoromethyl-2-indoloylguanidine

a) Preparation of ethyl 1-(3-tert-butoxycarbonylaminopropyl)-4-trifluoromethyl-2-indolecarboxylate

The reaction was carried out in a manner similar to Reference Example 5 (25) except for using 2.60 g (10.11 mmol) of ethyl 4-trifluoromethyl-2-indole-carboxylate, 0.445 g (11.12 mmol) of 60% sodium hydride, 4.32 g (15.17 mmol) of tert-butyl N-(3-iodopropyl)carbamate and 100 ml of dimethylformamide. Ethyl 1-(3-tert-butoxycarbonylaminopropyl)-4-trifluoromethyl-2-indolecarboxylate was thus obtained in an amount of 2.81 g (67.1%).

b) Preparation of 1-(3-aminopropyl)-4-trifluoromethyl-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 2.81 g (6.78 mmol) of ethyl 1-(3-tert-butoxycarbonylaminopropyl)-4-trifluoromethyl-2-indolecarboxylate, 6.48 g (67.8 mmol) of guanidine hydrochloride and 100 ml of a methanol solution of 3.66 g (67.8 mmol) of sodium methoxide. 1-(3-tert-Butoxycarbonylaminopropyl)-4-trifluoromethyl-2-indoloylguanidine was thus obtained in an amount of 2.83 g. This compound, 2.72 g, was treated in a manner similar to Example 114 to give 1.45 g (57.0%) of 1-(3-aminopropyl)-4-trifluoromethyl-2-indoloylguanidine hydrochloride.

M.P.: 245°C (decompsd.)

^{1}H NMR (DMSO-d_6) δ: 1.99-2.20 (2H, m), 2.70-2.89 (2H, m), 4.72 (2H, t, J=6.9Hz), 7.51-7.68 (2H, m), 8.06 (3H, br-s), 8.06-8.27 (2H, m), 8.71 (2H, br-s), 8.80 (2H, br-s), 12.30 (1H, br-s).

Example 141

Preparation of 1-(3-dimethylaminopropyl)-4-trifluoromethyl-2-indoloylguanidine

a) Preparation of ethyl 1-(3-dimethyaminopropyl)-4-trifluoromethyl-2-indolecarboxylate

Ethyl 1-(3-dimethylaminopropyl)-4-trifluoromethyl-2-indolecarboxylate was obtained in an amount of 1.77 g (74%) in a manner similar to Reference Example 5 except for using 2.07 g (4.84 mmol) of ethyl 4-trifluoromethyl-2-indolecarboxylate, 0.43 g (10.7 mmol) of 60% sodium hydride, 1.15 g (7.26 mmol) of 3-chloropropyldimethylamine hydrochloride and 80 ml of dimethylformamide.

b) Preparation of 1-(3-dimethylaminopropyl)-4-trifluoromethyl-2-indoloylguanidine

1-(3-Dimethylaminopropyl-4-trifluoromethyl-2-indoloylguanidine hydrochloride was obtained in an amount of 0.42 g (28%) in a manner similar to Example 1 except for using 1.77 g (3.45 mmol) of ethyl 1-(3-dimethylaminopropyl)-4-trifluoromethyl-2-indole-carboxylate, 3.30 g (34.5 mmol) of guanidine hydrochloride and 100 ml of a methanol solution of 1.87 g (34.5 mmol) of sodium methoxide.

M.P.: 252-255°C

^{1}H NMR (DMSO-d_6) δ: 2.07-2.30 (2H, m), 2.58-2.60 (6H, m), 3.00-3.19 (2H, m), 4.59-4.81 (2H, m), 7.49-8.67 (2H, m), 8.04-8.26 (2H, m), 8.71 (2H, br-s), 8.79 (2H, br-s), 10.69 (1H, br-s), 12.29 (1H, br-s).

The following compounds of Examples 142 to 147 were prepared in a manner similar to Example 141.

Example 142

1-(3-Dimethylaminopropyl)-2-indoloylguanidine hydrochloride:

Yield: 12.3%, M.P.: 240°C

^{1}H NMR (DMSO-d_6) δ: 2.04-2.27 (2H, m), 2.60-2.78 (6H, m), 2.98-3.17 (2H, m), 4.51-4.72 (2H, m), 7.12-7.28 (1H, m), 7.37-7.49 (1H, m), 7.75 (1H, d, J=8.3Hz), 8.07 (1H, s), 8.60 (2H, br-s), 8.81 (2H, br-s), 10.50 (1H, br-s), 12.15 (1H, br-s).

Example 143

4-Chloro-1-(3-dimethylaminopropyl)-2-indoloylguanidine hydrochloride:

Yield: 47.6%, M.P.: 237-240°C

^{1}H NMR (DMSO-d_6) δ: 2.07-2.27 (2H, m), 2.70 (6H, d, J=1.3Hz), 3.02-3.14 (2H, m), 4.55-4.72 (2H, m), 7.30 (1H, d, J=7.3Hz), 7.38-7.48 (1H, m), 7.77 (1H, d, J=8.6Hz), 8.06 (1H, s), 8.61 (2H, br-s), 8.68 (2H, br-s), 10.36 (1H, br-s), 12.11 (1H, br-s).

Example 144

1-[2-[(N-Pyrrolidinyl)ethyl]-2-indoloylguanidine hydrochloride:

Yield: 23.8%, M.P.: 236-239°C

^{1}H NMR (DMSO-d_6) δ: 1.75-2.11 (4H, m), 2.88-3.13 (2H, m), 3.40-3.68 (4H, m), 4.85-5.04 (2H, m), 7.16-7.29 (1H, m), 7.40-7.54 (1H, m), 7.78 (1H, d, J=7.9Hz), 7.87 (1H, d, J=7.9Hz), 8.10 (1H, s), 8.62 (2H, br-s), 8.81 (2H, br-s), 11.17 (1H, br-s), 12.24 (1H, br-s).

Example 145

4-Chloro-1-[2-(N-pyrrolidinyl)ethyl]-2-indoloylguanidine hydrochloride:

Yield: 6.1%, M.P.: 220°C

^{1}H NMR (DMSO-d_6) δ: 1.72-2.10 (4H, m), 2.83-3.13 (2H, m), 3.41-3.69 (4H, m), 4.86-5.05 (2H, m), 7.32 (1H, d, J=7.7Hz), 7.45 (1H, dd, J=8.3, 7.7Hz), 7.89 (1H, d, J=8.3Hz), 8.14 (1H, br-s), 8.67 (2H, br-s), 8.74 (2H, br-s), 11.35 (1H, br-s), 12.28 (1H, br-s).

Example 146

1-(3-Diethylaminopropyl)-4-trifluoromethyl-2-indoloylguanidine hydrochloride:

Yield: 30.8%, M.P.: 222-225°C

^{1}H NMR (DMSO-d_6) δ: 1.18 (6H, t, J=6.9Hz), 2.08-2.30 (2H, m), 2.92-3.20 (6H, m), 4.57-4.80 (2H, m), 7.50-7.65 (2H, m), 8.07-8.24 (2H, m), 8.66 (2H, br-s), 8.78 (2H, br-s), 10.58 (1H, br-s), 12.30 (1H, br-s).

Example 147

1-[2-(N-Morpholinyl)ethyl]-2-indoloylguanidine hydrochloride:

Yield: 20.5%, M.P.: 180°C

^{1}H NMR (DMSO-d_6) δ: 3.00-3.27 (2H, m), 3.27-3.70 (4H, m), 3.70-4.10 (4H, m), 4.88-5.14 (2H, m), 7.15-7.30 (1H, m), 7.39-7.52 (1H, m), 7.78 (1H, d, J=7.9Hz), 7.90 (1H, d, J=8.9Hz), 8.10 (1H, s), 8.65 (2H, br-s), 8.81 (2H, br-s), 11.85 (1H, br-s), 12.26 (1H, br-s).

Example 148

Preparation of 6-(3-aminopropoxy)-1-methyl-4-trifluoromethyl-2-indoloylguanidine

a) Preparation of ethyl 6-benzyloxy-1-methyl-4-trifluoromethyl-2-indolecarboxylate

Ethyl 6-benzyloxy-1-methyl-4-trifluoromethyl-2-indolecarboxylate was obtained in an amount of 2.25 g in a manner similar to Reference Example 5 except for using 2.20 g (6.06 mmol) of ethyl 6-benzyloxy-4-trifluoromethyl-2-indolecarboxylate, 0.24 g (6.06 mmol) of 60% sodium hydride, 1.72 g (12.1 mmol) of methyl iodide and 50 ml of dimethylformamide.

b) Preparation of ethyl 6-hydroxy-1-methyl-4-trifluoromethyl-2-indolecarboxylate

The reaction was carried out in a manner similar to Reference Example 15 a) except for using 2.23 g (5.91 mmol) of ethyl 6-benzyloxy-1-methyl-4-trifluoromethyl-2-indolecarboxylate, 0.3 g of 10% palladium/carbon and 50 ml of tetrahydrofuran. Ethyl 6-hydroxy-1-methyl-4-trifluoromethyl-2-indolecarboxylate was thus obtained in an amount of 1.70 g.

c) Preparation of ethyl 6-(3-tert-butoxycarbonylaminopropoxy)-1-methyl-4-trifluoromethyl-2-indolecarboxylate

The reaction was carried out in a manner similar to Reference Example 5 except for using 1.00 g (3.48 mmol) of ethyl 6-hydroxy-1-methyl-4-trifluoro-methyl-2-indolecarboxylate, 0.14 g (3.48 mmol) of 60% sodium hydride, 0.99 g (3.48 mmol) of tert-butyl N-(3-iodopropyl)carbamate and 40 ml of dimethylformamide. Ethyl 6-(3-tert-butoxycarbonylaminopropoxy)-1-methyl-4-trifluoromethyl-2-indolecarboxylate was thus obtained in an amount of 1.28 g.

d) Preparation of 6-(3-aminopropoxy)-1-methyl-4-trifluoromethyl-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 1.28 g (2.88 mmol) of ethyl 6-(3-tert-butoxycarbonylaminopropoxy)-1-methyl-4-trifluoro-methyl-2-indolecarboxylate, 5.50 g (57.6 mmol) of guanidine hydrochloride and 60 ml of methanol solution of 3.11 g (57.6 mmol) of sodium methoxide. 6-(3-tert-Butoxycarbonylaminopropoxy)-1-methyl-4-trifluoromethyl 2-indoloylguanidine was thus obtained in an amount of 0.41 g. This compound, 0.41 g, was treated in a manner similar to Example 114 to give 0.27 g (21.8%) of 6-(3-aminopropoxy)-l-methyl-4-trifluoro-methyl-2-indoloylguanidine hydrochloride.

M.P.: 272-274°C

^{1}H NMR (DMSO-d_6) δ: 2.08-2.13 (2H, m), 2.99-3.01 (2H, m), 4.05 (3H, s), 4.24-4.28 (2H, m), 7.21 (1H, s), 7.48 (1H, s), 7.97 (1H, s), 8.07 (3H, br-s), 8.56-8.70 (4H, m), 12.6 (1H, br-s).

The compound of Example 149 was obtained in a manner similar to Example 148.

Example 149

6-(3-Aminopropoxy)-1,4-dimethyl-2-indoloylguanidine hydrochloride:

M.P.: 265-267°C

^{1}H NMR (DMSO-d_6) δ: 2.04-2.09 (2H, m), 2.46 (3H, s), 2.96-2.99 (2H, m), 3.98 (3H, s), 4.13-4.18 (2H, m), 6.65 (1H, s), 6.91 (1H, s), 8.00-8.04 (4H, m), 8.44 (2H, br-s), 8.73 (2H, br-s), 11.92 (1H, br-s).

Example 150

Preparation of 6-(3-dimethylaminopropoxy)-1-methyl-4-trifluoromethyl-2-indoloylguanidine

a) Preparation of ethyl 6-(3-dimethylaminopropoxy)-1-methyl-4-trifluoromethyl-2-indolecarboxylate

Ethyl 6-(3-dimethylaminopropoxy)-1-methyl-4-trifluoromethyl-2-indolecarboxylate was obtained in an amount of 0.72 g in a manner similar to Reference Example 4 except for using 1.00 g (3.48 mmol) of ethyl 6-hydroxy-1-methyl-4-trifluoromethyl-2-indole-carboxylate, 0.35 g (8.70 mmol) of 60% sodium hydride, 0.82 g (5.22 mmol) of 3-chloropropyldimethylamine hydrochloride and 40 ml of dimethylformamide.

b) Preparation of 6-(3-dimethylaminopropoxy)-1-methyl-4-trifluoromethyl-2-indoloylguanidine

The reaction was carried out in a manner similar to Example 1 except for using 0.72 g (1.93 mmol) of ethyl 6-(3-dimethylaminopropoxy)-1-methyl-4-trifluoro-methyl-2-indolecarboxylate, 3.69 g (38.7 mmol) of guanidine hydrochloride and 50 ml of a methanol solution of 2.09 g (38.7 mmol) of sodium methoxide. 6-(3-dimethylaminopropoxy)-1-methyl-4-trifluoromethyl-2-indoloylguanidine was thus obtained in an amount of 0.40 g. This compound, 0.40 g, was treated in a manner similar to Example 1 to give 0.31 g (35.0%) of 6-(3-dimethylaminopropoxy)-1-methyl-4-trifluoro-methyl-2-indoloylguanidine hydrochloride.

M.P.: 264-265°C

^{1}H NMR (DMSO-d_6) δ: 2.17-2.23 (2H, m), 2.80 (6H, s), 3.2-3.4 (2H, m), 4.06 (3H, s), 4.23-4.27 (2H, m), 7.20 (1H, s), 7.50 (1H, s), 7.88 (1H, s), 8.5-8.7 (4H, m), 10.27 (1H, br-s), 11.90 (1H, br-s).

The compound of Example 151 was obtained in a manner similar to Example 150.

Example 151

1,4-Dimethyl-6-(3-dimethylaminopropoxy)-2-indoloylguanidine hydrochloride:

M.P.: 282-284°C

^{1}H NMR (DMSO-d_6) δ: 2.14-2.20 (2H, m), 2.46 (3H, s), 2.79-2.80 (6H, m), 3.1-3.3 (2H, m), 3.98 (3H, s), 4.13-4.17 (2H, m), 6.66 (1H, s), 6.93 (1H, s), 7.99 (1H, s), 8.42-8.74 (4H, m), 10.26 (1H, br-s), 11.85 (1H, br-s).

Experiment 1

Inhibition of Na^+/H^+ exchanger activity in vitro:

Method:

The experiment was performed by modifying the method of Yamori et al. described in J. Hypertension, 8, 153 (1990). That is, inhibition of the Na^+/H^+ exchanger activity was evaluated by the change in intracellular pH during acid loading, using the vascular smooth muscle cells isolated from the rat thoracic aorta.

Results:

The results of IC_{50} for the inhibition of the Na^+/H^+ exchanger activity tested are shown in Table 1 below.

Table 1

Compound	IC_{50} (μM)
Compound of Example 1	0.058
Compound of Example 8	0.05
Compound of Example 22	2.1
Compound of Example 29	0.0009
Compound of Example 55	0.02
Compound of Example 118	0.01
Dimethyl amiloride for comparison	0.60
5-Hexamethylene amiloride for comparison	0.14

Experiment 2

Inhibition of Na^+/H^+ exchanger activity in vitro

Method:

The experiment was performed by modifying the method of Mungre et al. described in Exp. Cell Res., 193, 236 (1991). That is, inhibition of the Na^+/H^+ exchanger activity was evaluated by the change in cell viability during acid loading, using the vascular smooth muscle cells isolated from the rat thoracic aorta.

Results:

The compounds of the present invention shown in Examples were evaluated by the minimum effective concentration (MEC) for the inhibition of the Na^+/H^+ exchanger activity. The results are shown in Table 2.

Table 2. Inhibition of Na^+/H^+ Exchanger Activity

Compound	Inhibition of Na^+/H^+ Exchanger MEC (μM)	Compound	Inhibition of Na^+/H^+ Exchanger MEC (μM)
Example 1	1.0	Example 25	0.3
Example 2	10	Example 26	0.3
Example 3	>10	Example 27	3.0
Example 4	>10	Example 28	>10
Example 5	0.03	Example 29	0.03
Example 6	0.3	Example 30	1.0
Example 7	0.3	Example 31	>10
Example 8	0.3	Example 32	>10
Example 9	0.1	Example 33	1.0
Example 10	10	Example 34	3.0
Example 11	0.3	Example 35	1.0
Example 12	0.3	Example 36	0.1
Example 13	1.0	Example 37	*
Example 14	>10	Example 38	3.0
Example 15	0.3	Example 39	0.3
Example 16	3.0	Example 40	1.0
Example 17	3.0	Example 41	1.0
Example 18	10	Example 42	10
Example 19	>10	Example 43	10
Example 20	1.0	Example 44	>10
Example 21	1.0	Example 45	>10
Example 22	0.3	Example 46	*
Example 23	0.3	Example 47	3.0
Example 24	0.3	Example 48	3.0

Table 2. cont'd

Compound	Inhibition of Na^+/H^+ Exchanger MEC (μM)	Compound	Inhibition of Na^+/H^+ Exchanger MEC (μM)
Example 49	3.0	Example 74	0.1
Example 50	1.0	Example 75	0.3
Example 51	1.0	Example 76	0.3
Example 52	1.0	Example 77	0.3
Example 53	1.0	Example 78	>10
Example 54	0.3	Example 79	3.0
Example 55	0.1	Example 80	3.0
Example 56	0.03	Example 81	>10
Example 57	1.0	Example 82	3.0
Example 58	0.3	Example 83	0.3
Example 59	1.0	Example 84	1.0
Example 60	*	Example 86	10
Example 61	0.3	Example 87	1.0
Example 62	>10	Example 88	>10
Example 63	0.3	Example 89	>10
Example 64	0.01	Example 90	10
Example 65	0.3	Example 91	3.0
Example 66	0.3	Example 92	0.3
Example 67	1.0	Example 93	1.0
Example 68	*	Example 94	1.0
Example 69	3.0	Example 95	0.003
Example 70	3.0	Example 96	0.03
Example 71	0.03	Example 97	>10
Example 72	0.1	Example 98	>10
Example 73	0.3	Example 99	10

Table 2. cont'd ...

Compound	Inhibition of Na^+/H^+ Exchanger MEC (μM)	Compound	Inhibition of Na^+/H^+ Exchanger MEC (μM)
Example 100	3.0	Example 122	0.03
Example 101	>10	Example 123	3.0
Example 102	10	Example 124	0.3
Example 103	>10	Example 125	0.01
Example 104	>10	Example 126	0.3
Example 105	*	Example 127	0.1
Example 106	*	Example 128	0.03
Example 107	0.1	Example 129	0.03
Example 108	>10	Example 130	0.03
Example 109	1.0	Example 131	0.1
Example 110	0.3	Example 132	0.1
Example 111	10	Example 133	1.0
Example 112	>10	Example 134	0.3
Example 113	3.0	Example 135	0.1
Example 114	1.0	Example 136	1.0
Example 115	>10	Example 137	>1
Example 116	>10	Example 138	3.0
Example 117	0.3	Example 139	3.0
Example 118	0.01	Example 140	1.0
Example 119	0.1	Example 85	10
Example 120	0.1	Dimethyl amiloride	3.0
Example 121	0.1	5-Hexamethylene amiloide	0.3

* : not measurable due to cytotoxicity

Experiment 3

Inhibition of Ischemia- and Reperfusion-induced Arrhythmia in vivo

Method:

The experiment was performed by modifying the method of Crome et al. described in J. Cardiovasc. Pharmacol., 8, 1249 (1986). That is, the prevention of arrhythmia induced by reperfusion after rat coronary artery occlusion was evaluated by the incidence of ventricular tachycardia and ventricular fibrillation as well as the mortality.

Results:

The compound of Example 1 in the present invention was evaluated by the method described above, with respect to the incidence of ventricular tachycardia and ventricular fibrillation, and mortality. The results are shown in Table 3 below.

Table 3. Inhibition of Reperfusion-induced Arrhythmia

Compound	Dose (mg/kg)	Incidence of Ventricular Tachycardia (%)	Incidence of Ventricular Fibrillation (%)	Mortality (%)
Example 1	0.3	50	0	0
	0.1	70	10	10
EIPA*	1	43	0	0
	0.3	100	56	44
Control**	–	100	95	76

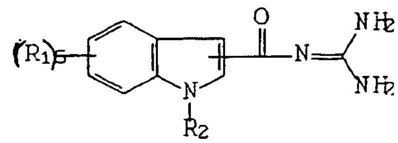
*EIPA : 5-N-ethyl-N-isopropyl amiloride

** Control: untreated

The indoloylguanidine derivatives of formula (1) inhibit the Na^+/H^+ exchanger activity and are useful for the prevention and treatment of diseases caused by the increased Na^+/H^+ exchanger activity, e.g., hypertension, cardiac ischemic reperfusion injury, arrhythmia, cerebral edema, cardiac hypertrophy, vascular lesions, atheroselerosis, etc.

Claims

1. An indoloylguanidine derivative of formula (1):



(1)

wherein

each R_1, which may be the same or different, is independently selected from hydrogen, an alkyl group, a substituted alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a halogen, a nitro group, an acyl group, a carboxyl group, an alkoxycarbonyl group, an aromatic group, and a group of formula: $-OR_3$, $-NR_6R_7$, $-SO_2NR_6R_7$ or $-S(O)_nR_{40}$;

R_2 is a hydrogen atom, an alkyl group, a substituted alkyl group, a cycloalkyl group, a hydroxy group, an alkoxy group or a group of formula $-CH_2R_{20}$;

R_3 is hydrogen, an alkyl group, a substituted alkyl group, a cycloalkyl group or a group shown by formula: $-CH_2R_{30}$, wherein R_{30} represents an alkenyl group or an alkynyl group;

each of R_6 and R_7, which may be the same or different, is independently selected from hydrogen, an alkyl group, a substituted alkyl group, a cycloalkyl group, an acyl group and a group of formula: $-CH_2R_{60}$, wherein R_{60} represents an alkenyl group or an alkynyl group; or R_6 and R_7, together with the nitrogen atom to which they are attached, form a saturated 5- to 7-membered cyclic amino group which optionally includes at least one other hetero atom in the ring;

R_{40} is an alkyl group or a substituted alkyl group;

n is 0, 1 or 2;

and,

R_{20} is an alkenyl group or an alkynyl group; and wherein the substituents R_1 and the guanidinocarbonyl group $-C(=O)-N=C(NH_2)_2$ are each, independently, attached to any one of the 5- and 6- membered rings of the indole nucleus;

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1, wherein

each R_1, which may be the same or different, is independently selected from hydrogen, an alkyl group, a substituted alkyl group, an alkenyl group, a cycloalkyl group, a halogen, a nitro group, an alkanoyl group, carboxyl group, an aryl group, an alkylsulfonyl group, and a group of formula $-OR_3$ or $-NR_6R_7$;

R_3 is hydrogen, an alkyl group or a substituted alkyl group;

each of R_6 and R_7, which may be the same or different, is independently selected from hydrogen, an alkyl group, a substituted alkyl group, an alkanoyl group or an aroyl group; or R_6 and R_7, together with the nitrogen atom to which they are attached, form a saturated 5- to 7-membered cyclic amino group which optionally includes at least one other hetero atom in the ring.

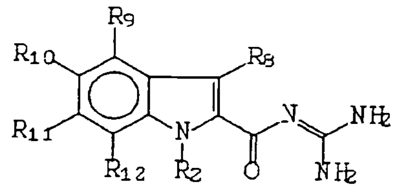
3. A compound according to claim 1 wherein each R_1, which may be the same or different, is independently selected from hydrogen, an alkyl group, a substituted alkyl group wherein the substituent is a hydroxy group or a group $-NR_6R_7$ wherein R_6 and R_7 are as defined in claim 1, a polyhaloalkyl group, an alkenyl group, a cycloalkyl group, a halogen, a nitro group, an alkanoyl group, a carboxyl group, a phenyl group, an alkylsulfonyl group or a group of formula $-OR_{31}$ wherein R_{31} is hydrogen, an alkyl group, or an alkyl group substituted with a hydroxy group, a carboxyl group, a phenyl group, a carbamoyl group, a mono- or dialkylcarbamoyl group or a group of formula $-NR_6R_7$ wherein R_6 and R_7 are as defined in claim 1.

4. A compound according to claim 1, wherein each R_1 which may be the same or different, is independently selected from an alkyl group, a polyhaloalkyl group, an alkenyl group, a halogen, a nitro group or a group of formula $-OR_{32}$ wherein R_{32} is hydrogen, an alkyl group or an alkyl group substituted by a hydroxy group, a carbamoyl group, a mono- or di-alkylcarbamoyl group or a group of formula: $-NR_6R_7$ wherein R_6 and R_7 are as defined in claim 1.

5. A compound according to any one of the preceding claims wherein R_2 is hydrogen, an alkyl group, a substituted alkyl group, a hydroxy group or an alkoxy group.

6. A compound according to any one of the preceding claims, which is a 2-indoloylguanidine compound.

7. An indoloylguanidine derivative of formula (2):



(2)

wherein

each of R_8, R_9, R_{10}, R_{11} and R_{12}, which may be the same or different, is independently selected from hydrogen, an alkyl group, a substituted alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a halogen, a nitro group, an acyl group, a carboxyl group, an alkoxycarbonyl group, an aromatic group, or a group shown of formula: $-OR_3$, $-NR_6R_7$, $-SO_2NR_6R_7$ or $-S(O)_nR_{40}$;

R_2 is hydrogen, an alkyl group, a substituted alkyl group, a cycloalkyl group, a hydroxy group, an alkoxy group or a group of formula: $-CH_2R_{20}$;

R_3 is hydrogen, an alkyl group, a substituted alkyl group, a cycloalkyl group or a group of formula: $-CH_2R_{30}$, wherein R_{30} represents an alkenyl group or an alkynyl group;

each of R_6 and R_7, which may be the same or different, is independently selected from hydrogen, an alkyl group, a substituted alkyl group, a cycloalkyl group, an acyl group and a group of formula: $-CH_2R_{60}$, wherein R_{60} is an alkenyl group or an alkynyl group; or R_6 and R_7, together with the nitrogen atom to which are they are attached, form a saturated 5- to 7-membered cyclic amino group which optionally includes at least one other heteroatom in the ring;

R_{40} is an alkyl group or a substituted alkyl group;

n is 0, 1 or 2; and

R_{20} is an alkenyl group or an alkynyl group; or a pharmaceutically acceptable acid addition salt thereof.

8. A compound according to claim 7, wherein R_8 is hydrogen and R_{10} is hydrogen or a halogen.

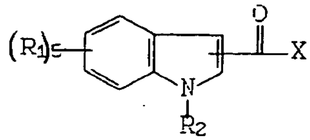
9. A compound according to claim 7 or 8, wherein R_9 is hydrogen, an alkyl group, a polyhaloalkyl group, a cycloalkyl, an alkenyl group, a halogen atom, a nitro group, an alkylsulfonyl group or a group of formula: $-OR_{33}$ wherein R_{33} is hydrogen, an alkyl group or an aralkyl group.

10. A compound according to any one of claims 7 to 9, wherein each of R_{11} and R_{12} which may be the same or different, is independently selected from hydrogen, an alkyl group, a substituted alkyl group wherein the substituent is a hydroxy group or a group $-NR_6R_7$, a polyhaloalkyl group, an alkenyl group, a cycloalkyl group, a halogen, a nitro group, or a group of formula: $-OR_3$ or $-NR_6R_7$.

11. A compound according to any one of claims 7 to 10, wherein R_2 is hydrogen, an alkyl group, a substituted alkyl group, a hydroxy group or an alkoxy group.

12. A process for the preparation of an indoloylguanidine derivative, or a salt thereof, as defined in claim 1, the process comprising

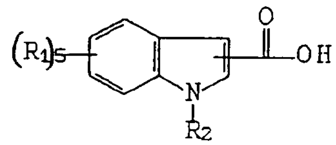
(a) reacting a derivative of indolecarboxylic acid of the following formula (3):



(3)

wherein R_1 and R_2 are as defined in claim 1 and X is a leaving group, with guanidine in an inert solvent; or

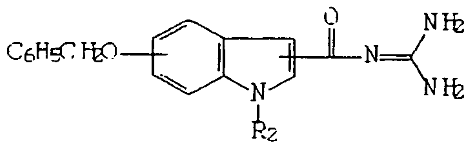
(b) reacting an indolecarboxylic acid of the following formula (4):



(4)

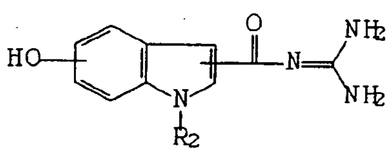
wherein R_1 and R_2 are as defined in claim 1, with guanidine in an inert solvent; or

(c) subjecting a compound of formula (5):



(5)

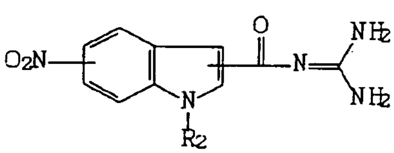
wherein R_2 is as defined in claim 1, to debenzylation, so as to obtain an indoloylguanidine derivative of formula (Ia):



(Ia)

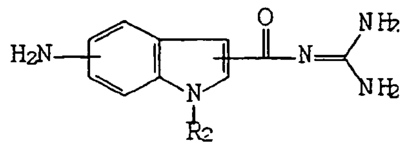
wherein R_2 is as defined in claim 1; or

(d) reducing a compound of formula (6):



(6)

wherein R_2 is as defined in claim 1, so as to obtain an indoloylguanidine derivative of formula (Ib):



(Ib)

wherein R_2 is as defined in claim 1; and/or, if desired,
(e) converting a compound of formula (I), prepared by any of the above processes (a) to (d), into a pharmaceutically acceptable salt.

13. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier or diluent and, as an active principal, a compound as claimed in any one of claims 1 to 11.

14. A compound as defined in any of claims 1 to 11 for use in a method of treatment of the human or animal body by therapy.

15. Use of a compound as defined in any one of claims 1 to 11 in the manufacture of a medicament for the treatment of a disease caused by increased Na^+/H^+ exchanger activity.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 3101

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
A	DE-A-41 27 026 (BOEHRINGER) *Table 1: compound no. 2* * page 6, line 12 - line 30; claims * ---	1-15	C07D209/42 A61K31/40
A D	EP-A-0 416 499 (HOECHST AG) * the whole document * & JP-A-3 106 858 (HOECHST AG) ---	1-15	
A	MERCK INDEX, 11TH EDITION, 1989 , RAHWAY N.J. USA page 67 S. BUDAVARI *abstract nr. 417: Amiloride* ---	1-15	
A	EP-A-0 116 360 (KALI-CHEMIE PHARMA GMBH) * page 22 - page 23; claims 1,12; examples * -----	1-15	

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	29 July 1994	Bosma, P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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